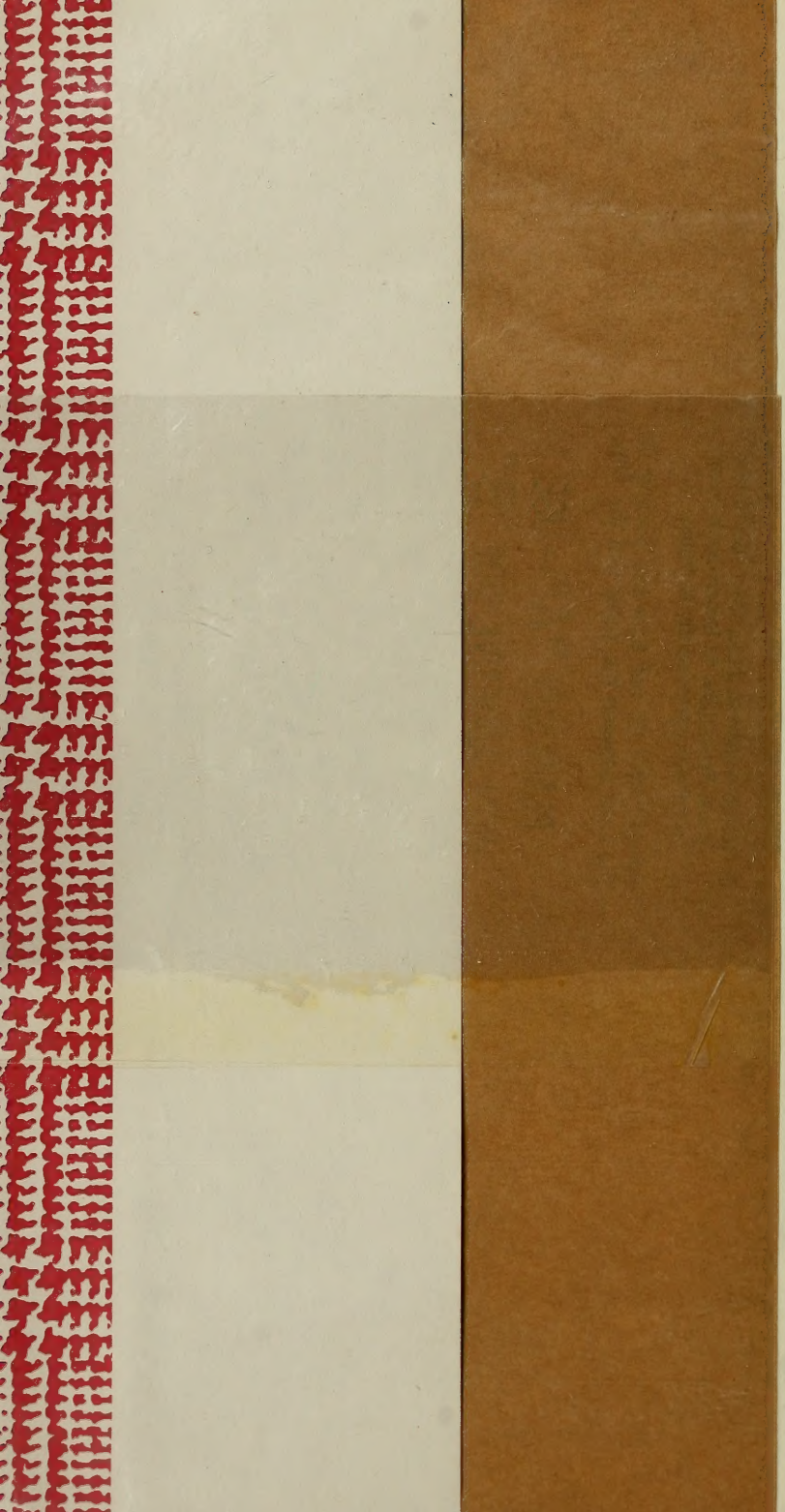

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SYMPOSIUM
on the
Treatment of Diabetic Retinopathy

Edited by: Morton F. Goldberg, M.D.
Consultant in Ophthalmology
U.S. Public Health Service

Stuart L. Fine, M.D.
Medical Consultant
U.S. Public Health Service

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Foreword

The increase in diabetic retinopathy as a major cause of blindness has prompted the Public Health Service to concern itself with the effectiveness of current therapy. Hundreds of persons have undergone pituitary ablation and photocoagulation, yet it remains to be demonstrated unequivocally that either of these modalities does, in fact, constitute effective treatment. Problems in evaluation of therapy are difficult under the best of circumstances; but when one is dealing with a disease characterized by spontaneous remissions and exacerbations, one must be cautious before pronouncing that any therapeutic modality exerts a beneficial effect upon the course of the disease.

Diabetes is the second leading cause of new adult blindness in the United States today. It has advanced to this position due to the prolonged life expectancy of diabetics, which has resulted from improved medical management of the disease. Of those blinded by diabetes, 84 percent owe their disability to retinopathy. Indeed, retinopathy now constitutes one of the most dreaded vascular complications which the diabetic patient must anticipate. Whereas 25 percent of juvenile onset diabetics have evidence of nephropathy after 15 to 20 years of diabetes mellitus, more than 60 percent have retinopathy. Furthermore, in contrast to other leading causes of blindness (cataracts and glaucoma) which primarily affect individuals in the older age groups, those blind from diabetes are in the third, fourth, and fifth decades of life. For example, the average patient who has been subjected to a hypophysectomy is aged 35 and has had diabetes for 20 years.

A review of existing knowledge led us to believe that an international symposium could make significant contributions towards developing a system of classification and a method of patient evaluation which would be widely accepted. At the least, the communications gap among investigators representing diverse clinical disciplines could be bridged. As one might have predicted for a symposium of this nature, more questions were raised than were answered, but perhaps this is as it should be. It is hoped, however, that this monograph will initiate a new phase of clinical investigation by facilitating more effective communication among physicians concerned with the management of this disorder. It is our hope that this symposium will provide a framework for future cooperative studies seeking to elucidate the natural course

of the disease and the effects of pituitary ablation and photocoagulation.

We should like to pay special tribute to the steering committee (Drs. Matthew D. Davis, chairman; Robert F. Bradley, Edward Okun, and William H. Sweet) for assisting in the selection of participants, planning of the agenda, and guiding the direction of the symposium; to all participants for their enormous contributions to the conference and to this monograph; and to the editors (Drs. Morton F. Goldberg and Stuart L. Fine) for their initiative and industry in making this entire effort possible.

Clifford H. Cole, M.D.,
Chief, Neurological and Sensory Disease Control Program.

Glen McDonald, M.D.,
Chief, Diabetes and Arthritis Control Program.

Contents

	Page
Foreword	v
Steering Committee	xiv
Participants	xv
Preface	xix
O'Hare Classification	xxi

PART I: CLASSIFICATION

Chapter

1. Practical Experience With a Method for Grading Diabetic Retinopathy 3
   N. W. Oakley, G. F. Joplin, E. M. Kohner, and *T. R. Fraser*
2. Airlie Classification of Diabetic Retinopathy 7
   M. D. Davis, E. W. D. Norton, and *Frank L. Myers*

Discussion of Classification 23
Moderator: *W. P. Beetham* and *M. D. Davis*

PART II: NATURAL HISTORY AND VISUAL PROGNOSIS

3. Diabetic Retinopathy as a Cause of Visual Impairment 41
   F. I. Caird
4. Clinical Observations Concerning the Pathogenesis of Diabetic Retinopathy 47
   M. D. Davis, F. L. Myers, R. L. Engerman, G. de Venecia, and *Y. L. Magli*
5. Evolution of Lesions in Proliferative Diabetic Retinopathy: an 8 Year Photographic Survey 55
   J. H. Dobree
6. The Natural History of Diabetic Retinopathy 65
   E. M. Kohner and *C. T. Dollery*
7. The Natural Course of Diabetic Retinopathy: A Clinical Study of 321 Eyes Followed One Year or More 81
   F. L. Myers, M. D. Davis, and *Y. L. Magli*
8. Visual Prognosis in Advanced Diabetic Retinopathy .. 87
   A. Patz and *J. W. Berkow*

Chapter *Page*

9. Summary of Papers on Natural History 93
M. D. Davis

10. Summary of Papers on Visual Prognosis 97
A. Patz

Discussion of Natural History and Visual Prognosis 99
Moderator: *W. Beetham*

PART III: RELATIONSHIP OF RETINOPATHY TO METABOLIC CONTROL

11. Control of Diabetes and Diabetic Retinopathy 107
F. I. Caird

12. The Control of Diabetes Mellitus and the Progression of Retinopathy 115
H. C. Knowles, Jr.

13. The Effect of Diabetic Control on Diabetic Retinopathy 119
E. M. Kohner, T. R. Fraser, G. F. Joplin, and *N. W. Oakley*

14. Summary of Papers on Relationship of Retinopathy to Metabolic Control 129
H. C. Knowles, Jr.

Discussion of Relation of Retinopathy to Metabolic Control 132
Moderator: *K. Lundbaek*

PART IV: PITUITARY ABLATION

15. Pituitary Ablation and Diabetic Retinopathy in Perspective: An Historical Summary 147
R. A. Field

16. Fluorescein Photography in Proliferative Diabetic Retinopathy Treated by Pituitary Ablation. 153
M. C. Balodimos, S. B. Rees, L. M. Aiello, R. F. Bradley, and *A. Marble*

17. Surgical Pituitary Ablation for Diabetic Retinopathy 171
R. F. Bradley and *S. B. Rees*

18. Some Technical Observations on Surgical Hypophysectomy in the Treatment of Diabetic Retinopathy 193
C. A. Fager

Chapter *Page*

19. Radiofrequency Pituitary Coagulation for Angiopathic Diabetic Retinopathy 203
R. A. Field, T. Behrendt, N. T. Zervas, P. D. Gordy, and *T. D. Duane*
20. Hypophyseal Stalk Section for Angiopathic Diabetic Retinopathy 213
R. A. Field, J. W. McMeel, W. H. Sweet, and *C. L. Schepens*
21. Pituitary Ablation for the Treatment of Diabetic Retinopathy 227
E. J. Greenberg, B. S. Ray, A. G. Pazianos, W. L. Peretz, M. Isaacs, and *B. J. Koren*
22. Transsphenoidal Microsurgical Selective Anterior Pituitary Ablation: A Pathophysiological Investigation of Diabetic Retinopathy 235
J. Hardy, A. Panisset, A. Marchildon, A. Lanthier
23. Pituitary Suppression in Diabetic Retinopathy by Proton Bean in Surgically "Unfit" Patients 249
R. M. Kjellberg, J. W. McMeel, V. McManus and *A. M. Koehler*
24. Metabolic and Ophthalmological Observations Following Heavy Particle Pituitary Suppressive Therapy in Diabetic Retinopathy 277
J. A. Linfoot, J. L. Born, J. F. Garcia, E. Manougian, R. Kling, C. Y. Chong, C. A. Tobias, R. A. Carlson, and *J. H. Lawrence*
25. Hypophysectomy for Diabetic Angiopathy: A Controlled Clinical Trial 291
K. Lundbaek, R. Malmros, H. C. Andersen, J. H. Rasmussen, E. Bruntse, P. H. Madsen, and *V. A. Jensen*
26. Hypophyseal Stalk Section as Treatment for Diabetic Retinopathy: Ocular Aspects 313
J. W. McMeel
27. The Treatment of Diabetic Retinopathy by Pituitary Implantation of Radioactive Yttrium 317
N. W. Oakley, G. F. Joplin, E. M. Kohner, R. Blach, M. Hartog, and *T. R. Fraser*
28. Pituitary Ablation in the Treatment of Diabetic Retinopathy 331
O. H. Pearson, C. H. Thomas, B. Kaufman, C. N. Shealy, W. F. Collins, Jr., J. Jane, and *C. C. R. Jackson*
29. Cryohypophysectomy and Diabetic Retinopathy 341
N. H. Roth, R. W. Rand, D. A. Adams, G. Heuser, A. M. Dashe, J. Hanley, and *J. Gold*

Chapter *Page*

30. Pituitary Stalk Section for Angiopathic Diabetic Retinopathy: Technique, Mortality, Morbidity, and Post-Operative Management 355
W. H. Sweet and *R. A. Field*

31. Radiofrequency Pituitary Ablation: Its use in Diabetic Retinopathy 365
N. T. Zervas, P. D. Gordy, and *R. A. Field*

32. Summary of Ocular Aspects of Papers on Pituitary Ablation 375
J. W. McMeel

Discussion of Ocular Aspects of Pituitary Ablation 380
Moderator: *B. Becker*

33. Summary of Medical Aspects of Papers on Pituitary Ablation 395
R. F. Bradley

Discussion of Medical Aspects of Pituitary Ablation 400
Moderator: *T. R. Fraser*

34. Summary of Surgical Aspects of Papers on Pituitary Ablation 415
W. H. Sweet

Discussion of Ocular Aspects of Pituitary Ablation 422
Moderator: *B. S. Ray*

PART V: PHOTOCOAGULATION

35. Ruby Laser Photocoagulation in Treatment of Diabetic Proliferating Retinopathy: Preliminary Report 437
L. M. Aiello, W. P. Beetham, M.C. Balodimos, B. I. Chazan, and *R. F. Bradley*

36. Photocoagulation Therapy of Diabetic Retinopathy 465
G. W. Cleasby

37. Light Coagulation in Proliferative Diabetic Retinopathy 479
J. H. Dobree

38. The Role of Photocoagulation in the Therapy of Proliferative Diabetic Retinopathy 485
G. S. Harris and *P. K. Rentiers*

39. Photocoagulation in Proliferative Diabetic Retinopathy: A Preliminary Report 495
H.-W. Larsen

Chapter *Page*

40. Photocoagulation as a Treatment of Diabetic Retinopathy 507
J. W. McMeel and *W. A. J. van Heuven*
41. Photocoagulation of Diabetic Retinopathy 515
C. B. Mortimer
42. Role of Photocoagulation in the Treatment of Proliferative Diabetic Retinopathy: Continuation and Follow-up Studies (359 Eyes of 283 Patients) ... 523
E. Okun and *G. P. Johnston*
43. Light Coagulation as an Adjunct to Cryohypophysectomy 537
N. H. Roth and *R. W. Rand*
44. Photocoagulation of Diabetic Retinopathy: A Rationale 545
H. F. Spalter
45. Photocoagulation for Retinitis Proliferans 555
P. R. Thornfeldt
46. Vitreous Studies in Diabetic Retinopathy Treated with Photocoagulation 559
W. A. J. van Heuven
47. The Treatment of Diabetic Retinopathy 563
R. B. Welch
48. Results of Photocoagulation in Diabetic Retinopathy 569
A. K. Wessing and *G. Meyer-Schwickerath*
49. A Review of 232 Patients Including 401 Eyes with Diabetic Retinopathy Treated by Light Coagulation 593
P. C. Wetzig and *C. N. Jepson*
50. The Treatment of Diabetic Retinopathy by Laser Photocoagulation 603
H. C. Zweng
51. Summary of Visual and Anatomic Results from Papers on Photocoagulation 607
B. R. Straatsma

Discussion of Visual and Anatomic Results of Photocoagulation 612
Moderator: *I. Leopold*
52. Summary of Treatment Techniques from Papers on Photocoagulation 623
E. Okun

Chapter *Page*

DISCUSSION OF TREATMENT TECHNIQUES OF PHOTOCOAGULATION 630
Moderator: *P. C. Wetzig*

PART VI: MISCELLANEOUS TOPICS

53. NET VASCULAR PRESSURE RATIOS IN DIABETIC RETINOPATHY 657
T. D. Duane, T. Behrendt and *R. A. Field*
54. EFFECT OF THE RUBY LASER ON THE MONKEY RETINA: AN ELECTRON MICROSCOPIC STUDY (ADDENDUM TO PAPER BY AIELLO ET AL. CHAPTER 35) 665
T. Kuwabara and *L. Aiello*
55. FLUORESCENCE MICROSCOPIC, AUTORADIOGRAPHIC AND HISTOCHEMICAL STUDIES ON HUMAN DIABETIC AND NON-DIABETIC EYES 673
H. W.-Larsen and *A. U. Werner*
56. ERG IN JUVENILE DIABETES: A PROGNOSTIC STUDY 681
Sv. E. Simonsen
57. A COMPARISON OF METHODS OF TREATMENT FOR DIABETIC RETINOPATHY 691
A. M. Koehler, R. N. Kjellberg, and *J. W. McMeel*
58. PROLIFERATIVE DIABETIC RETINOPATHY: COMPARISON OF VISUAL RESULTS IN VARIOUS TREATMENT CATEGORIES 701
M. D. Davis and *F. L. Myers*

EPILOGUES

1. REVIEW OF SELECTED ASPECTS OF DIABETIC RETINOPATHY 713
R. F. Bradley
2. SUMMARY OF PERSONAL IMPRESSIONS OF AIRLIE HOUSE SYMPOSIUM ON DIABETIC RETINOPATHY 718
M. D. Davis
3. PHOTOCOAGULATION FOR DIABETIC RETINOPATHY 720
E. Okun
4. PRODUCTION OF HYPOPITUITARISM IN THE TREATMENT OF DIABETES 722
W. H. Sweet and *R. A. Field*

APPENDICES

Appendix *Page*

A. *E. M. Kohner, T. R. Fraser, G. F. Joplin, N. W. Oakley (Chapter 13)* 733
B. *R. A. Field, T. Behrendt, N. T. Zervas, P. D. Gordy, T. D. Duane* (Chapter 19) 741
C. *E. J. Greenberg, B. S. Ray, A. G. Pazianos, W. L. Peretz, M. Isaacs, B. J. Koren* (Chapter 21) 745
D. *J. Hardy, A. Panisset, A. Marchildon, A. Lanthier* (Chapter 22) 750
E. *R. N. Kjellberg, J. W. McMeel, V. McManus, A. M. Koehler* (Chapter 23) 753
F. *O. H. Pearson, C. H. Thomas, B. Kaufman, C. N. Shealy, W. F. Collins, Jr., J. Jane, C. C. R. Jackson* (Chapter 28) 764
G. *N. H. Roth, R. W. Rand, D. A. Adams, G. Heuser, A. M. Dashe, J. Hanley, J. Gold* (Chapter 29) 770
H. *J. H. Dobree* (Chapter 37) 775
I. *G. S. Harris, P. K. Rentiers* (Chapter 38) 780
J. *C. B. Mortimer* (Chapter 40) 784
K. *E. Okun, G. P. Johnston* (Chapter 42) 789
L. *N. H. Roth, R. W. Rand* (Chapter 43) 819
M. *H. F. Spalter* (Chapter 44) 822
N. *P. C. Wetzig, C. N. Jepson* (Chapter 49) 830

Index 857

Steering Committee

Chairman
Matthew D. Davis, M.D.
Division of Ophthalmology
University of Wisconsin Medical Center
1300 University Avenue
Madison, Wis. 53706

Robert F. Bradley, M.D.
The Joslin Clinic
15 Joslin Road
Boston, Mass. 02215

Edward Okun, M.D.
Department of Ophthalmology
Washington University School of Medicine
St. Louis, Mo. 63110

William H. Sweet, M.D., D. Sc.
Division of Neurosurgery
The Massachusetts General Hospital
Boston, Mass. 02114

Symposium Participants

Lloyd Aiello, M.D.
108 Bay State Road,
Boston, Mass. 02215

Marios Balodimos, M.D.
Elliott P. Joslin Research Laboratory
170 Pilgrim Road
Boston, Mass. 02215

Bernard Becker, M.D.
Department of Ophthalmology
Washington University School of Medicine
660 South Euclid Avenue
St. Louis, Mo. 63108

William P. Beetham, M.D.
108 Bay State Road
Boston, Mass. 02215

Rolf K. Blach, M.D., F.R.C.S.
Senior Lecturer in Clinical Ophthalmology
Moorsfield Eye Hospital
City Road, London, E.C.I. England

Francis I. Caird, D.M., M.R.C.P.
Department of Geriatric Medicine
University of Glasgow, Stobhill General Hospital
Glasgow, N. 1, Scotland

Gilbert W. Cleasby, M.D.
Presbyterian Hospital of Pacific Medical Center
2400 Clay Street
San Francisco, Calif. 94115

William Coxe, M.D.
Division of Neurosurgery
Washington University School of Medicine
St. Louis, Mo. 63110

Frank Davidoff, M.D.
Director, Diabetes Unit
Beth Israel Hospital
330 Brookline Avenue
Boston, Mass. 02215

John H. Dobree, M.D., F.R.C.S.
Surgeon in Charge
Department of Ophthalmology
St. Bartholomew's Hospital
113 Harley Street
London, W. 1, England

Thomas D. Duane, M.D.
Department of Ophthalmology
The Jefferson Medical College
1025 Walnut Street
Philadelphia, Pa. 19107

Charles A. Fager, M.D.
Department of Neurosurgery
Lahey Clinic Foundation
Lahey Clinic Division
605 Commonwealth Avenue
Boston, Mass. 02215

Richard A. Field, M.D.
Department of Medicine
Jefferson Medical College of Philadelphia
1025 Walnut Street
Philadelphia, Pa. 19107

T. Russell Fraser, M.D., F.R.C.P.
Department of Medicine
Postgraduate Medical School
DuCane Road
London, W. 12, England

Ernest Greenberg, M.D.
Sloan-Kettering Institute for Cancer Research
York Avenue and 68th Street
New York, N.Y. 10021

Jules Hardy, F.R.C.S. (C), F.A.C.S.
Department of Neurosurgery
Notre Dame Hospital
University of Montreal
1396 est., rue Sherbrooke
Montreal 24, P.Q., Canada

Gordon S. Harris, M.D.
Suite 507
750 West Broadway
Vancouver 9, British Columbia, Canada

Wichard van Heuven, M.D.
Department of Ophthalmology
University of Albany Medical School
Albany, N.Y. 12208

John A. Jane, M.D.
Division of Neurosurgery
University Hospitals
Case Western Reserve University
2065 Adelbert Road
Cleveland, Ohio 44106

Glen P. Johnston, M.D.
Queeny Tower Building
Suite 5103
4989 Barnes Hospital Plaza
St. Louis, Mo. 63110

Graham F. Joplin, Ph. D., M.R.C.P.
Department of Medicine
Postgraduate Medical School
DuCane Road
London, W. 12, England

Harry Keen, M.D., M.R.C.P.
Reader in Medicine
Department of Medicine
Guy's Hospital Medical School
London, S.E.1, England

Raymond N. Kjellberg, M.D.
Division of Neurosurgery
Massachusetts General Hospital
Boston, Mass. 02214

Harvey C. Knowles, Jr., M.D.
President
American Diabetes Association
Department of Internal Medicine
Cincinnati General Hospital
Cincinnati, Ohio 45229

Eva M. Kohner, B.Sc., M.B, M.R.C.P.
Department of Medicine
Postgraduate Medical School
DuCane Road, London, W. 12, England

Hans-Walther Larsen, M.D.
Barsehoj 16
Hellerup, Denmark

Irving H. Leopold, M.D.
Department of Ophthalmology
Mount Sinai School of Medicine
Fifth Avenue and 100th Street
New York, N.Y. 10029

Harvey Lester, M.D.
Department of Ophthalmology
University Hospitals
Case Western Reserve University
2065 Adelbert Road
Cleveland, Ohio 44106

John A. Linfoot, M.D.
Donner Laboratory & Donner Pavilion
University of California
Berkeley, Calif. 94720

Prof. Knud Lundbaek, M.D.
Aarhus University School of Medicine
Aarhus, Denmark

J. Wallace McMeel, M.D.
Retina Associates
99 West Cedar Street
Boston, Mass. 02114

Clive B. Mortimer, M.A., M.B., B. Chir. F.R.C.S. (C)
Suite 1001
Medical Arts Building
170 St. George Street
Toronto 5, Ontario, Canada

Frank L. Myers, M.D.
Division of Ophthalmology
University of Wisconsin Medical Center
1300 University Avenue,
Madison, Wisc. 53706

Edward W. D. Norton, M.D.
Department of Ophthalmology
Bascom Palmer Eye Institute
University of Miami School of Medicine
1638 N.W. 10th Avenue
Miami, Fla. 33136

Nigel Oakley, M.B., Ch.B., M.R.C.P.
Department of Medicine
Middlesex Hospital
London, W. 1, England

Robert Packman, M.D.
Department of Medicine
Washington University School of Medicine
St. Louis, Mo. 63110

Arnall Patz, M.D.
The Wilmer Institute
The Johns Hopkins Hospital
Baltimore, Md. 21205

Olof H. Pearson, M.D.
Department of Medicine
University Hospitals
Case Western Reserve University
2065 Adelbert Road
Cleveland, Ohio 44106

Walter L. Peretz, M.D.
Department of Ophthalmology
New York Hospital—Cornell Medical Center
525 East 68th Street
New York, N.Y. 10021

Robert W. Rand, M.D., Ph. D.
Division of Neurosurgery
University of California School of Medicine
Los Angeles, Calif. 90024

Bronson Ray, M.D.
Division of Neurosurgery
New York Hospital—Cornell Medical Center
525 East 68th Street
New York, N.Y. 10021

Nathan Roth, M.D.
960 E. Green Street,
Pasadena, Calif. 91101

Robert A. Schimek, M.D.
Ochsner Clinic
1514 Jefferson Highway
New Orleans, La. 70121

Svend E. Simonsen, M.D.
University Eye Clinic
Rigshospitalet Tagensvej
Tagensvej 18
Copenhagen NV. Denmark

Harold F. Spalter, M.D.
Institute of Ophthalmology of the Presbyterian Hospital
College of Physicians & Surgeons of Columbia University
635 West 165th Street
New York, N.Y. 10011

333-611 O—69——2

Bradley R. Straatsma, M.D.
Department of Ophthalmology
Jules Stein Eye Institute
University of California School of Medicine
Los Angeles, Calif. 90024

Paul R. Thornfeldt, M.D.
919 South West Taylor Street
Portland, Oreg. 97205

Robert Welch, M.D.
The Wilmer Institute
The Johns Hopkins Hospital
Baltimore, Md. 21205

Paul C. Wetzig, M.D.
Post Office Box 2170
Colorado Springs, Colo. 80901

Priv. Doz. Dr. Achim Wessing
Hufelandstrasse 55
43 Essen—Holsterhausen, Germany

Nicholas T. Zervas, M.D.
Division of Neurosurgery
Beth Israel Hospital
330 Brookline Avenue
Boston Mass. 02215

H. Christian Zweng, M.D.
Palo Alto Medical Clinic
300 Homer Avenue
Palo Alto, Calif. 94301

Preface

On September 29 to October 1, 1968, an international Symposium on the Treatment of Diabetic Retinopathy, sponsored by the U.S. Public Health Service, was held at Airlie House, Warrenton, Va. A steering committee representing the disciplines of ophthalmology (Drs. Matthew D. Davis and Edward Okun), internal medicine (Dr. Robert F. Bradley), and neurosurgery (Dr. William H. Sweet) provided invaluable assistance in the selection of participants and agenda topics. In general, the subject matter of the symposium was limited to clinical and therapeutic considerations in order to insure an adequate opportunity for extensive discussion.

Manuscripts and data were submitted in advance. Subsequent distribution of duplicated copies to all participants, one month prior to the meeting, provided an opportunity for each person to review carefully the materials of all other participants before engaging in discussions at the symposium itself. These manuscripts appear as numbered chapters within this monograph, and their accompanying data appear in the appendices.

The symposium was divided into six sessions: (1) classification of diabetic retinopathy; (2) natural history and visual prognosis of diabetic retinopathy; (3) relationship of retinopathy to metabolic control; (4) pituitary ablation; (5) photocoagulation; and (6) miscellaneous topics of interest. Each session began with a summarization of all manuscripts submitted on the subject. These summaries are presented as chapters 9, 10, 14, 15, 32, 33, 34, 51, and 52. The summary on classification of retinopathy is found in chapter 2. Each summary was followed by a general discussion, in which individuals who had submitted papers on the subject participated as panelists. These discussions are found following the summary chapters. At the conclusion of the symposium, members of the steering committee were requested to submit their overall impressions of the current state of therapy directed towards diabetic retinopathy. These impressions are found in the epilogues.

Several items deserve particular attention. First, the O'Hare classification of diabetic retinopathy on page XXI requires study in order to make more meaningful the references to it in the various chapters, summaries, and discussions. Second, chapters 57 and 58, submitted

after the symposium, represent an attempt by the respective authors to compare various methods of treatment on the bases of the raw data available. The reader may wish to review carefully these data (listed in the table of contents as appendices) in order to draw his own conclusions regarding the relative merits of a given therapeutic modality. Finally, the Airlie Classification, described in chapter 2, is proposed for use in future prospective studies to facilitate comparison of data among physicians and centers investigating the natural history of, or the effects of therapy on, diabetic retinopathy.

We wish to thank Mrs. Helen Longen for verification and standardization of the bibliographical citations and Mrs. Lena Jones and Miss Kathy Jones for their assistance in preparation of the manuscript. We are especially indebted to Dr. Clifford H. Cole, Chief of the Neurological and Sensory Disease Control Program, and to Dr. Glen McDonald, Chief of the Diabetes and Arthritis Control Program, for the constant support and encouragement given us while organizing the symposium and this monograph.

Morton F. Goldberg, M.D.
Stuart L. Fine, M.D.

A Note on the O'Hare Classification of Diabetic Retinopathy

An essential ingredient for evaluation of therapeutic results among different centers is a standard classification insuring that patients in similar stages of a disease are compared. The lack of such a classification in diabetic retinopathy has meant that despite extensive experience with pituitary ablative procedures, photocoagulation, and various medical regimens—all alleged to exert beneficial effects upon diabetic retinopathy—no meaningful comparison could be made.

It was considered that a standard classification would be essential in analyzing and comparing data to be presented by a variety of investigators at the U.S. Public Health Service Symposium on the Treatment of Diabetic Retinopathy. In an attempt to remedy this problem, a group [1] met at the O'Hare Inn, Des Plaines, Ill., on June 29, 1968, to devise a classification scheme which would be used for the symposium. It was obligatory to propose a system which was sufficiently broad to permit retrospective classification of data and sufficiently detailed to provide meaningful separation between groups of eyes. Although it was not intended that this classification would be universally acceptable, it is noteworthy that three of the seven O'Hare participants (Drs. Davis, McMeel, and Okun) who had previously authored considerably more detailed classifications, were willing to use the O'Hare classification in place of their own. The classification which follows was used retrospectively by most groups reporting at this symposium.

O'Hare Classification of Diabetic Retinopathy

Four characteristics are considered: (1) Background retinopathy; (2) vitreous hemorrhage; (3) new vessels; and (4) fibrous proliferation extending into the vitreous.

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[1] Drs. M. D. Davis, S. L. Fine, M. F. Goldberg, J. W. McMeel, E, W. D. Norton, E. Okun, and P. Wetzig.

B—This category includes patients with all degrees of diabetic retinopathy excluding proliferative changes.

"B" or "background" includes microaneurysms, hemorrhages, exudates, and venous abnormalities. The presence of even the smallest amount of proliferative tissue places a patient into a different category, as will be evident from the following notes.

H_0—No vitreous hemorrhage.

H_1—Presence of vitreous hemorrhage, but the retina can be seen well enough to be classified.

H_2—This category describes eyes with a vitreous hemorrhage which is so extensive that the retina cannot be seen well enough to be classified.

N_1—Four or fewer discrete patches and four of fewer disc areas of new vessels.

N_2—Greater than four discrete patches or greater than four disc areas of new vessels.

F_0—No fibrous proliferation extending into the vitreous cavity. (There may be some fibrous proliferation present but it is restricted to the surface of the retina.)

F_1—Fibrous proliferation extends into the vitreous cavity, but involves four or fewer discrete patches and four or fewer disc areas.

F_2—Greater than four discrete patches or greater than four disc areas of fibrous proliferation extending into the vitreous.

After looking at your photographs, drawings, diagrams, or verbal descriptions, it should be possible to characterize the retina of each patient according to the following scheme. By various combinations of designated symbols, one can arrive at the following 15 categories.

B—There is background retinopathy but no proliferative tissue, neither neovascular nor fibrous.

B H_1—Background retinopathy.
No neovascular tissue visible.
No fibrous proliferation visible.
Vitreous hemorrhage is present.

H_2—Vitreous hemorrhage obscures the retina so that it cannot be classified.

N_1 F_0 H_0—Four or fewer discrete patches and four or fewer disc areas of new vessels.
No fibrous proliferation extending into the vitreous.
No vitreous hemorrhage.

N_1 F_0 H_1—Four or fewer discrete patches and four or fewer disc areas of new vessels.

No fibrous proliferation extending into the vitreous.

Vitreous hemorrhage is present but does not prevent classification of the retina.

N_1 F_1 H_0—Four or fewer discrete patches and four or fewer disc areas of new vessels.

Four or fewer discrete patches and four or fewer disc areas of fibrous tissue extending into the vitreous.

No vitreous hemorrhage.

N_1 F_1 H_1—Four or fewer discrete patches and four or fewer disc areas of new vessels.

Four or fewer discrete patches and four or fewer disc areas of fibrous tissue extending into the vitreous.

Vitreous hemorrhage is present but does not prevent classification of the retina.

N_1 F_2 H_0—Four or fewer discrete patches and four or fewer disc areas of new vessels.

Greater than four discrete patches or greater than four disc areas of fibrous tissue extending into the vitreous.

No vitreous hemorrhage.

N_1 F_2 H_1—Four or fewer discrete patches and four or fewer disc areas of new vessels.

Greater than four discrete patches or greater than four disc areas of fibrous tissue extending into the vitreous.

Vitreous hemorrhage is present but does not prevent classification of the retina.

N_2 F_0 H_0—Greater than four discrete patches or greater than four disc areas of new vessels.

No fibrous tissue extending into the vitreous.

No vitreous hemorrhage.

N_2 F_0 H_1—Greater than four discrete patches or greater than four disc areas of new vessels.

No fibrous tissue extending into the vitreous.

Vitreous hemorrhage is present but does not prevent classification of the retina.

N_2 F_1 H_0—Greater than four discrete patches or greater than four disc areas of new vessels.

Four or fewer discrete patches and four or fewer disc areas of fibrous tissue extending into the vitreous.

No vitreous hemorrhage.

N_2 F_1 H_1—Greater than four discrete patches or greater than four disc areas of new vessels.
Four or fewer discrete patches and four or fewer disc areas of fibrous tissue extending into the vitreous.
Vitreous hemorrhage is present but does not prevent classification of the retina.

N_2 F_2 H_0—Greater than four discrete patches or greater than four disc areas of new vessels.
Greater than four discrete patches or greater than four disc areas of fibrous tissue extending into the vitreous.
No vitreous hemorrhage.

N_2 F_2 H_1—Greater than four discrete patches or greater than four disc areas of new vessels.
Greater than four discrete patches or greater than four disc areas of fibrous tissue extending into the vitreous.
Vitreous hemorrhage is present but does not prevent classification of the retina.

PART I

Classification

CHAPTER 1

Practical Experience with a Method for Grading Diabetic Retinopathy

NIGEL W. OAKLEY, M.D., Ch. B., M.R.C.P.
GRAHAM F. JOPLIN, Ph. D., M.R.C.P.
EVA M. KOHNER, B. Sc., M.B., M.R.C.P.
T. RUSSELL FRASER, M.D., F.R.C.P.

INTRODUCTION

If highly effective therapies for diabetic retinopathy were available, the establishment of their value would not require special techniques for assessing the progress of the condition; and if the natural history of the untreated disease were predictable, less effective therapeutic measures could be evaluated without difficulty. Unfortunately, however, the natural history of retinopathy is still so unpredictable that recognizable improvements can rarely be reliably attributed to any particular form of therapy. For this reason a method of grading various features of diabetic retinopathy, amenable to statistical analysis, was devised 3 years ago in connection with work assessing the therapeutic value of pituitary ablation. For details of the Hammersmith grading system, the reader is referred to the original description (*1*). Five features of diabetic retinopathy have been defined, and fundus photographs are graded in terms of these parameters by comparison with a selected set of standard Kodachrome fundus pictures. The five features are (1) hemorrhages and microaneurysms, (2) new vessels, (3) venous irregularities, (4) hard exudates, and (5) fibrous retinitis proliferans. Each of these can be graded on a 0–5 scale of increasing severity, assessments for individual photographic fields being averaged to provide a value for the whole eye.

Validity of the Method

It was previously shown (*1*) that physicians and ophthalmologists concerned in development of the grading technique could assess fundus photographs with a high degree of consistency, although significant variations appeared in the evaluation of venous irregularities. Other diabetologists, unfamiliar with the technique, were provided with printed instructions, standard photographs, and a set of 15 test transparencies, and also made consistent assessment for four

Department of Medicine, Royal Postgraduate Medical School, London W.12, England.

parameters, but assigned widely varying grades for venous irregularities. It was concluded that widespread acceptance of such a grading system could lead to improvement in understanding and communication between different centers interested in diabetic retinopathy and encourage cooperative ventures in this field of study; it was also hoped that this system might prove useful for recording progress of diabetic retinopathy in eyes under serial observation. Sets of standard photographs, with instructions for use, were accordingly made available at cost price ($5) and have been requested and distributed as follows: United Kingdom, 15; United States, 9; Switzerland, 3; Germany, 2; Australia, 2; Italy, 2; South Africa, 1; Malta, 1; Greece, 1; and Brazil, 1.

Grading Individual Photographs

Experience with the grading system has confirmed that individual photographs can usually be graded consistently by independent assessors, particularly when they are experienced with the technique. The following notes summarize our findings with respect to the individual parameters:

Microaneurysms

These are graded in terms of the number of lesions; their size is not relevant and care must be taken to avoid overgrading fields with small numbers of large blot hemorrhages and undergrading those showing large numbers of microaneurysms.

New vessels

The most important problem in grading new vessels is the distinction between true neovascularization and capillary abnormalities, with dilatation and areas of vascular closure. At present, all visible abnormal vascular channels are classified together as new vessels, but fluorescein studies suggest that it may not be entirely valid to do this. Another problem relates to the status of neovascular fronds, often arising from the optic disc, and extending forward into the vitreous. It must be assumed that these fronds are supported by a fine network of fibrous tissue, and it is difficult to formulate a dividing line between new vessels and retinitis proliferans when assessing this type of lesion. At present, only new vessels which develop in relation to preexisting fibrous retinitis proliferans are excluded from assessment.

Venous irregularities

These are assessed in terms of both the percentage of visible veins thought to be abnormal and the severity of the abnormalities. Grading this parameter is always difficult, and is subject to considerable observer variation. As originally defined, to facilitate grading, generalized dilatation, which is difficult to assess, is not an irregularity—a ruling which is open to criticism.

Hard exudates

Owing to their confluent nature these lesions are assessed in terms of the area of retina affected. This is slightly more difficult than the numerical method used for microaneurysms, but has given no serious interpretive problems.

Retinitis proliferans

This has conveniently been defined as preretinal fibrous tissue, and the main grading problem occurs in patients with extensive spreading neovascularization, in association with which a good quality photograph will frequently reveal a veil of connective tissue lying on the surface of the retina. This must be regarded as the earliest evidence of retinitis proliferans and graded as such. Fibrous tissue far forward in the vitreous may also present grading problems unless pictures are taken with several planes of focus.

Grading Eyes

Any number of individual photographic fields may be assessed in an eye, but where, as is usually the case, these fields are to be averaged to give an "eye grade" and care must be taken to avoid overlapping fields; these may result in one fundal feature being assessed twice, and thus given double its true numerical importance. In practice this has proved a considerable problem and it is often easiest to ascribe lesions on or close to the optic disc to particular standard fields according to a predetermined convention. It is never admissible to assess an eye on the basis of less than two photographic fields, and if one field out of three or four becomes unassessable during serial observation, spurious changes in "eye grade" can be minimized by carrying forward the last valid grade of the lost field into subsequent assessments (vide infra).

Serial Assessments

Many special problems arise when serial assessments are made on the same eye, to follow retinal progress. Firstly, valid serial gradings can only be made on photographs of comparable technical quality covering identical retinal fields. Thus progressive vitreous haze, large retinal and preretinal hemorrhages and distortion of retinal topography by contracting fibrous retinitis proliferans may all present real problems. Secondly, particular care must be taken not to record spurious improvements by failing to appreciate the natural history of the disease. This consideration is particularly relevant in the case of new vessels, which may be replaced by fibrous retinitis proliferans without any real improvement in the retinal condition. It has been found necessary to "freeze" the grading of new vessels when, for this reason, it becomes no longer possible to assess deterioration or improvement. This solution to the problem is not entirely satisfactory, but at least it prevents the recording of unreal improvements, even in mean "eye grades."

Although the grading method was devised for assessing features of retinopathy in absolute terms, by reference to standard photographs, the shortcomings of the technique must be recognized and accepted. Thus it is the authors' practice, when making serial assessments on single fields, never to record a change of grade without directly comparing the relevant serial pictures to ensure that such a change is justified; in this way the chance of recording spurious changes is minimized.

Conclusion

The Hammersmith Hospital grading system has been in use for 3 years and provides a satisfactory method for grading selected features of diabetic retinopathy, using nonstereoscopic fundus photographs. When the method is used for serial studies, additional sources of error appear, some of which are discussed above.

Reference

1. Oakley, Nigel and others: Diabetic retinopathy. I. The assessment of severity and progress by comparison with a set of standard fundus photographs. Diabetologia 3: 402–405, August 1967.

CHAPTER 2

The Airlie Classification of Diabetic Retinopathy

Formulated and proposed by the Committee on Classification consisting of E. W. D. Norton, M. D. Davis, S. L. Fine, J. Glaser, M. F. Goldberg, G. P. Johnston, E. M. Kohner, J. W. McMeel, F. L. Myers, N. Oakley, E. Okun, and P. C. Wetzig.

Text and illustrations
prepared and submitted by

MATTHEW D. DAVIS, M.D.
EDWARD W. D. NORTON, M.D.
FRANK L. MYERS, M.D.[1]

The meaningful exchange of data among scientists is predicated upon communication through common usage of standardized signs and symbols, that is, a mutually understood language. While disciplines such as electronics and chemistry are eminently suited for uniform quantitative descriptions, clinical medicine in general is not. More specifically, no valid system to record information obtained by ophthalmoscopy has been available to permit qualitative and quantitative analysis of findings in the ocular fundus. In an effort to facilitate the retrospective and prospective analysis of patients by conferring some degree of uniformity on the critical evaluation of diabetic retinopathy, a meeting was held June 29, 1968, at O'Hare Inn, Des Plaines, Ill.

The "O'Hare Classification" (*1*) was formulated to enable participants in the subsequent Airlie House symposium to prepare case material for presentation incorporating a basic, although skeleton, system of categorization of the lesions seen in diabetic retinopathy. As an

[1] In this chapter the authors have attempted to set forth the consensus of the small group of participants who met twice to discuss the classification of diabetic retinopathy. At the first meeting in June 1968 the "O'Hare classification" (p. XXI) was formulated. During the Airlie House symposium the group met again and reached tentative agreement on the principles of the classification which follows. In attempting to formalize the deliberations of this group and to select the required photographic standards, the format of the classification has undergone several minor changes. Publication deadlines have prevented submission of the manuscript to all members of the committee, and the authors must therefore assume sole responsibility for these changes as well as their share of responsibility for the chapter's other shortcomings. Only time will determine whether this classification will indeed provide a useful common language for clinicians and investigators working in this field. If so, the credit belongs to all members of the committee, particularly those who have brought to it their extensive experience with previous classifications of their own design (*2, 3, 4*). Several members of the committee plan to test the classification during the coming year, and to report their impressions of it. It is anticipated that, if necessary, a revision will be published.

expediency in view of time limitations, certain deficiencies in classification were accepted, particularly pertaining to the early nonproliferative phase of retinopathy. However, in reviewing the data that were presented, it was clear that even with gross inadequacies the O'Hare Classification was valuable in comparing the results obtained by various therapeutic procedures at several different medical centers. With this encouragement, the committee on classification developed a more comprehensive scheme to critically describe diabetic retinopathy and to evaluate the influence of treatment modalities. The importance of this undertaking becomes clear when one considers that no valid conclusions may yet be derived despite 1,200 recorded pituitary ablations and more than 1,600 recorded photocoagulation procedures performed on diabetics during the last 10 years.

It is intended that serious investigators of diabetic retinopathy will prospectively employ this current classification system in future studies and will use it at least as a framework upon which may be constructed more detailed classifications fitted to particular needs. A suitable classification derived by subjective and objective methods should therefore include the facility to (1) describe qualitatively and quantitatively the status of diabetic retinopathy at initial and subsequent examinations, and to record permanently by fundus photography lesions in certain predesignated areas; (2) provide a "common language" to enable investigators to exchange and examine objectively prepared material; (3) establish the natural course of diabetic retinopathy by statistical analysis of serial examinations; (4) evaluate by serial examinations the influence of a variety of therapeutic measures.

Of fundamental importance in the classification of diabetic retinopathy are the basic skills with which each ophthalmoscopist examines the ocular fundus. Those procedures considered vital include the following:

(1) *Ophthalmoscopy*—While direct ophthalmoscopy may be satisfactory for classification of the posterior pole in the nonproliferative phase, binocular indirect ophthalmoscopy is desirable for evaluation of the proliferative course of diabetic retinopathy.

(2) *Slit-lamp biomicroscopy*—Using either the Hruby or corneal contact lens, the slit lamp provides a highly magnified, binocular view of the fundus details essential for classification of "early" diabetic retinopathy and recognition of the vitreoretinal relationships.

(3) *Fundus photography*—To obtain objective data for classification, four specific predetermined areas of the ocular fundus should be photographed (fig. 1). Area 5 is desirable but considered optional

because of technical difficulties in photography. Stereoscopic fundus photography is unquestionably more desirable and should be used wherever possible.

(4) *Fluorescein fundus angiography*—This procedure is essential in the study of nonproliferative retinopathy and greatly enhances the study of the early proliferative phase. It is recognized that techniques will vary widely among different investigators depending upon particular interests, but in general fluorescein angiography will be used primarily to evaluate intraretinal microvascular abnormalities, considered by some to be typical of severe progressive ("florid") retinopathy. These abnormalities are variously interpreted as dilated preexisting capillaries, "shunt" vessels, fusiform aneurysms, or intraretinal neovascularization. It is recommended that for routine use a photograph of area No. 2 (fig. 1), in the 15- to 25-second post injection arteriovenous phase be evaluated for the above vascular changes as well as for microaneuryms. In addition, the leakage of fluorescein at 3 to 5 minutes should be photographically assessed in areas 1, 2, 3, and 4. (As greater experience is accumulated, it is probable that a more detailed fluorescein classification will evolve.)

(5) *Fundus diagrams*—Diagrammatic records of areas of neovascularization and fibrous proliferation are considered a useful adjunct to any study of proliferative retinopathy and are strongly encouraged. Drawings overlaid by transparent tracing paper provide the best currently available method for the accurate recording of changes in the retina and posterior vitreous observed by slit-lamp examination and indirect binocular ophthalmoscopy (preferably using the +14 diopter lens).

The committee is well aware that many institutions making significant contributions to the study of diabetic retinopathy are not equipped to carry out all of the above recommended techniques of examination. However, it would seem that for meaningful participation in any objective collaborative study, fundus photography as outlined in item (3) above, is the absolute minimum.

The committee carefully studied several previous classifications (*2*, *3*, *4*, *5*), some using standard photographs for grading each type of lesion and others using written definitions and diagrams. In the former, individual photographic fields of eyes to be classified were compared with standard photographs, while in the latter, the appearance of the fundus as a whole was classified using written definitions of grades at the time of ophthalmoscopy or by referring later to a fundus diagram. The obvious advantage of a classification based on photographs is its objectivity and suitability for collaborative studies utilizing central

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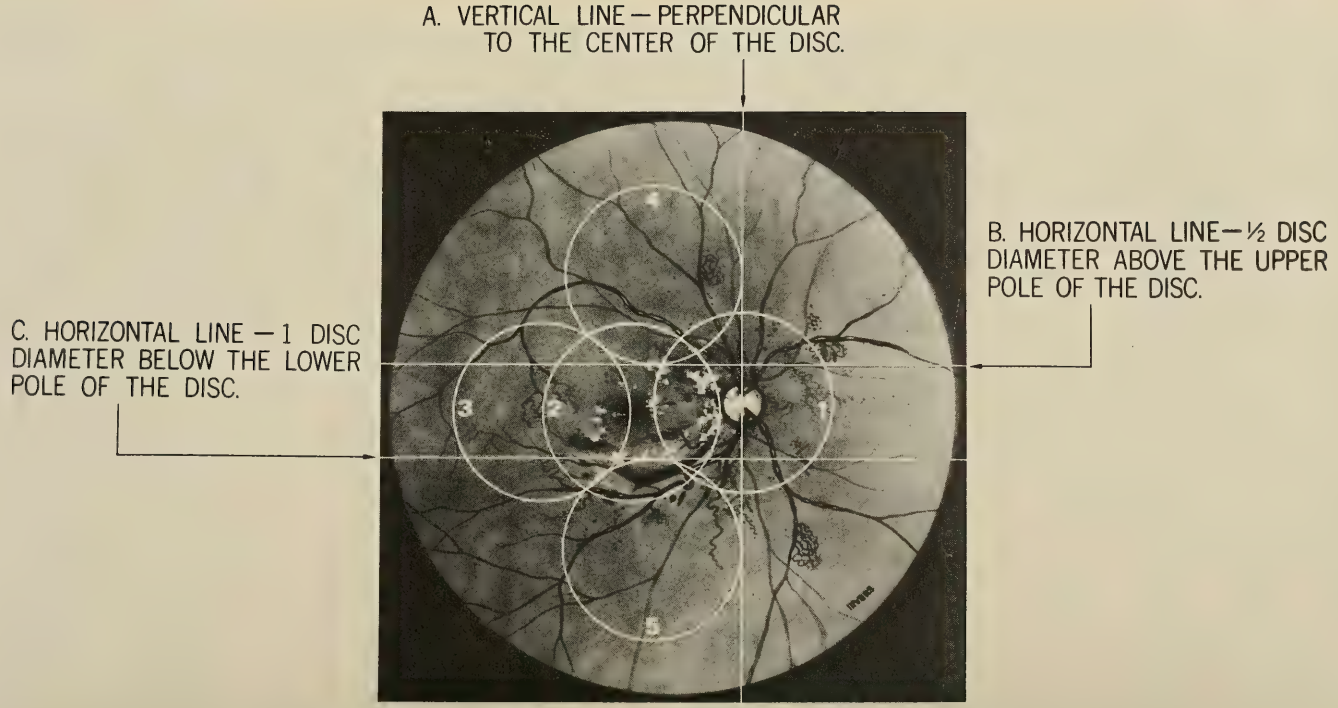
A. VERTICAL LINE — PERPENDICULAR TO THE CENTER OF THE DISC.
B. HORIZONTAL LINE — ½ DISC DIAMETER ABOVE THE UPPER POLE OF THE DISC.
C. HORIZONTAL LINE — 1 DISC DIAMETER BELOW THE LOWER POLE OF THE DISC.
1
2
3
4
5

FIGURE 1.—*Photographic fields as recorded with the Zeiss fundus camera:*

Area 1—Centered on optic disc;
Area 2—Centered on macula;
Area 3—Nasal limit tangent to macula, i.e. area covered temporal to macula;
Area 4—Nasal limit tangent to perpendicular line through center of disc; inferior limit tangent to horizontal line one-half disc diameter above the upper pole of the optic disc;
Area 5—Nasal limit tangent to perpendicular line through center of disc; upper limit tangent to horizontal line 1 disc diameter below the lower pole of the optic disc.

FIGURE 2.—*Hemorrhages and/or microaneurysms*

All punctate, blot or linear hemorrhages and all microaneurysms, whether the color of venous blood or more pale, with or without a recognizable wall, are considered, excluding only hemorrhages that are clearly pre-retinal (Figs. 7A and B). Judge the number of lesions present.

FIGURE 3.—*Hard exudate*

All (deep) "hard" white or yellowish-white deposits with sharp margins are included, whether punctate or confluent, in circinate pattern, perivenous, or at areas of localized retinal elevation. Judge area of retina involved.

FIGURE 4.—*Venous abnormalities*

Localized variation in caliber (beading) is the major feature to be assessed. Diffuse increase in caliber is not included, as it is considered too nonspecific and difficult to evaluate. Judge length of vein involved and severity of beading. One or more venous loops without beading should be graded 1, as should venous sheathing.

FIGURE 5.—*Intraretinal microvascular abnormalities*

Dilated tortuous intraretinal vascular segments are the principal lesions considered. Punctate microaneurysms and new vessels clearly on the surface of the retina are not included. Judge area of retina involved.

FIGURE 6.—*Neovascularization and fibrous proliferation within 1 D.D. of disc*

New vessels and fibrous proliferations on the surface of the retina or farther forward in the vitreous cavity located over the disc or within one disc diameter from the disc in any direction are considered. Surface neovascularization may be difficult to differentiate from intraretinal microvascular abnormalties in nonstereo photographs. New vessels which can be clearly seen to cross over large retinal vessels are usually true surface new vessels rather than intraretinal microvascular abnormalities. Judge area involved. Classify new vessels and fibrous proliferations separately. Arrows point to new vessels.

FIGURE 7.—*Pre-retinal hemorrhage* FIGURE 7A.

Both boat-shaped hemorrhages with a fluid level (7A) and roughly round, confluent or linear patches of hemorrhage (7B) just anterior to the retina are included. If either type equals or exceeds these standards, the grade is 2. Judge area of retina involved.

FIGURE 7B.

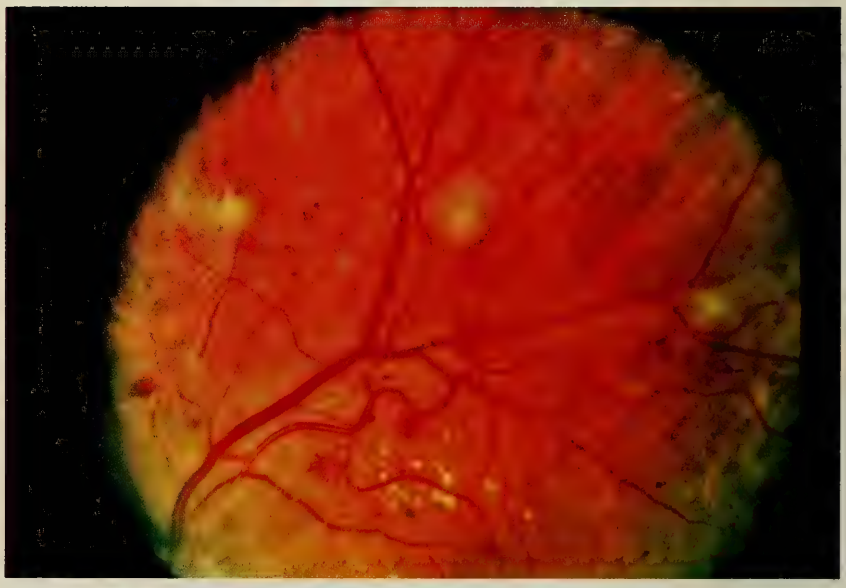

FIGURE 8.—*Soft "exudates" (cotton wool patches)*

All superficial white or gray-white deposits with ill defined edges or striations parallel to the nerve fibers are counted. At times these lesions are intensely white, but more frequently they are faint as is the patch above the center of this photograph.

FIGURE 11.—*Neovascularization other areas of retina*

All clear-cut new vessels on the surface of the retina or further forward in the vitreous are considered. Judge area involved and number of patches. In this photograph most of the new vessels in the upper right hand quadrant of the field should be disregarded because they are within 1 D.D. of the disc. This photograph contains two patches of new vessels which occupy approximately 2 to 2½ disc areas.

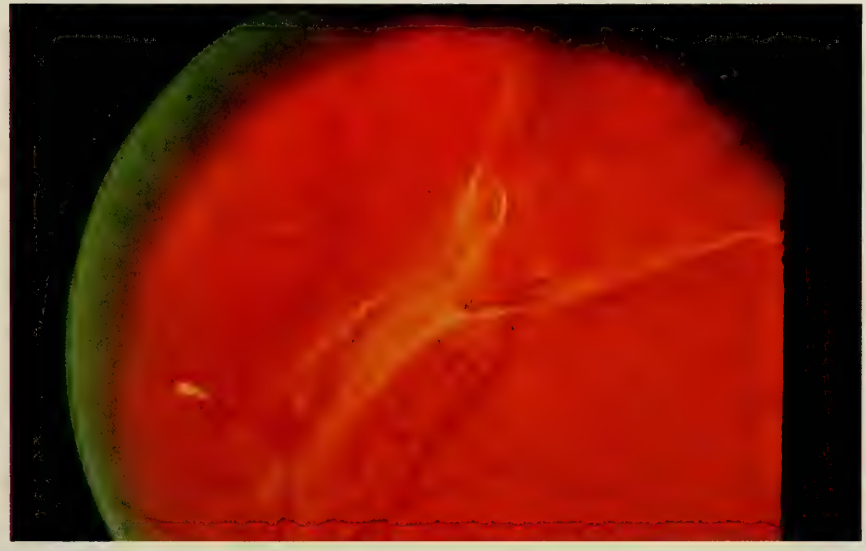

FIGURE 12.—*Fibrous proliferation other areas of retina*

Any clearly visible "fibrous" tissue either accompanying new vessels or occasionally without visible new vessels is considered. The density of the tissue, that is whether it is opaque and white or thin and almost transparent, is of less importance than the area covered. In this photograph, the density of the proliferation is moderate, and the area covers approximately two disc areas. Judge area involved and number of patches.

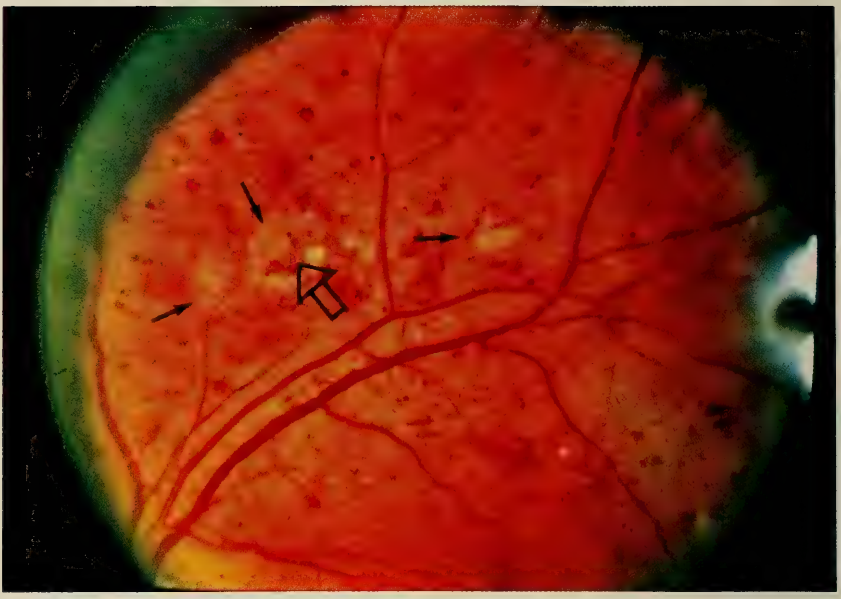

FIGURE 13.—*Example for grading (See Table IV)*
Arrows indicate "soft exudates". Open arrow indicates intraretinal microvascular abnormalities.

FIGURE 14.—*Example for grading (See Table IV).*

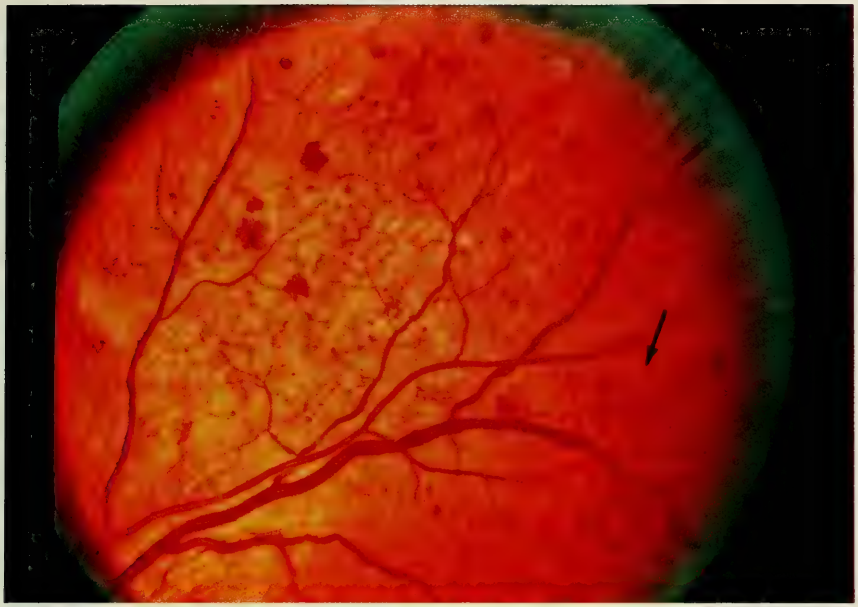

FIGURE 15.—*Example for grading (See Table IV)*
Arrow points to a single patch of new vessels on the surface of the retina. All other abnormal small vessels are intraretinal microvascular abnormalities.

FIGURE 16.—*Example for grading (See Table IV)*
The preretinal hemorrhage arises from what is no doubt a patch of fibrovascular proliferation, but no unequivocal new vessels can be seen.

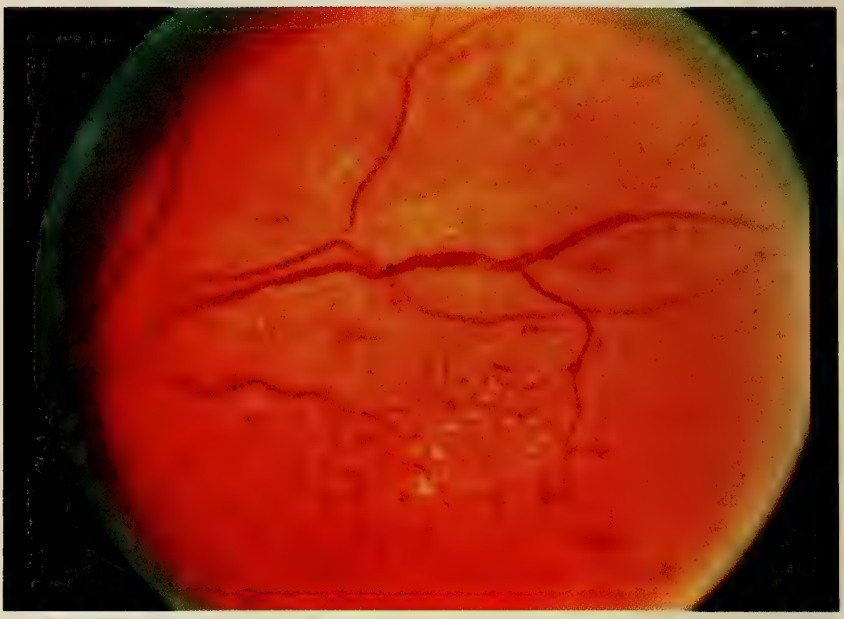

FIGURE 17.—*Example for grading* (*See Table IV*)

FIGURE 18.—*Example for grading* (*See Table IV*)

readers. Its greatest weakness is the likelihood of missing important findings which lie outside of the predetermined photographic fields. This consideration is of particular importance in proliferative retinopathy since important areas of neovascularization and fibrous proliferation frequently lie outside of the preselected photographic fields. It was concluded that a combination of both methods—photographic and ophthalmoscopic—would be superior to either alone.

The lesions to be considered are included in table I and definitions for grading are given. In order to provide simplicity and reproducibility among different centers, it was felt that the grades of the various lesions should be restricted to three: None ("0"), mild to moderate ("1"), and moderate to severe ("2"). Two techniques for defining grades have been used: (1) *Standard photographs* are provided for the grading of hemorrhages and/or microaneurysms, hard exudates, and other lesions for which grades of severity would be difficult to define except in comparison to a standard photograph. A single standard photograph of each type of lesion is provided and, for the sake of simplicity, is compared with the most severely involved ophthalmoscopic field of comparable area of the eye to be classified. In general, if the patient's retinopathic changes are considered less severe than the standard example, they will be classified as "grade 1"; if equal to or worse than the standard, as "grade 2." Fortunately the area of the fundus seen in one ophthalmoscopic field with the binocular indirect ophthalmoscope using the +14 diopter lens closely approximates the 30° field of the Zeiss fundus camera, simplifying comparison between them. If the photograph is examined with magnification, however, there is a risk of underestimating the extent of the abnormalities in the fundus under examination unless direct ophthalmoscopy with its greater magnification is also used. (2) *Written descriptions* specifying the number and/or size of the lesions are to be utilized to evaluate findings such as new vessels, fibrous proliferation, and retinal elevations.

As indicated above, table I is a summary of the grading definitions Certain points require further elaboration. Separate color photographic standards are provided for hemorrhages and/or microaneuryms (fig. 2), "hard" exudates (fig. 3), venous abnormalities (fig. 4), "intraretinal microvascular abnormalities" (fig. 5), neovascular and fibrous proliferation within one disc diameter of the disc (fig. 6) and preretinal hemorrhage (fig. 7a–7b).

In the case of hemorrhages and/or microaneurysms, the *number* of lesions in the standard photograph is the major factor to be evaluated. Since hard exudates are frequently confluent, the *area* covered is emphasized.

TABLE I.—*Summary of grading definitions*

Lesion	Grade 0	Grade 1	Grade 2
A. NONPROLIFERATIVE [1]			
Hemorrhaghes and/or microaneurysms.	None	Present but not as severe as standard photograph (fig. 2).	As severe or worse than standard photograph.
"Hard exudates"	do	Present, but not as severe as standard photograph (fig. 3).	Do.
"Soft exudates"	do	1 to 4 in entire fundus.	5 or more in entire fundus.
Venous abnormalities.	do	Present, but not as severe as standard photograph (fig. 4).	As severe or worse than standard photograph.
Intraretinal microvascular abnormalities.	do	Present, but not as severe as standard photograph (fig. 5).	Do.
Retinal edema (at macula).	do	Covers less than 1 disc area.	Covers 1 disc area or more.
B. FLUORESCEIN			
Arteriovenous phase (15 to 25 seconds).	Normal	Intraretinal microvascular abnormalities and microaneurysms less than standard (fig. 9).	Abnormalities as severe as or worse than standard.
Late phase (3 to 5 minutes).	No dye leakage.	Dye leakage less less than standard photograph (fig. 10).	Dye leakage equal to or worse than standard photograph.
C. PROLIFERATIVE			
Neovascularization within 1 disc-diameter of disc.	None	Present, but not as severe as standard photograph (fig. 6).	As severe or worse than standard photograph.
Neovascularization areas other than disc.	do	1 to 4 discrete patches and 4 or less disc areas of new vessels.	5 or more discrete patches or more than 4 disc areas of new vessels.
Fibrous proliferation within 1 disc-diameter of disc.	do	Present, but not as severe as standard photograph (fig. 6).	As severe or worse than standard photograph.
Fibrous proliferation areas other than disc.	do	1 to 4 discrete patches and 4 or less disc areas.	5 or more discrete patches or more than 4 disc areas.
Plane of proliferation.	Within ¼ disc diameter of surface of attached retina.	Anterior to retina's normal position by ¼ to 2 disc diameters.	Anterior to retina's normal position by 2 disc diameters or more.
Retinal elevation	None	4 or less disc areas in extent.	More than 4 disc areas in extent.

See footnote at end of table.

TABLE I.—*Summary of grading definitions*—Continued

Lesion	Grade 0	Grade 1	Grade 2
D. VITREOUS HEMORRHAGE			
Preretinal hemorrhage	do	Present but not as severe as standard photograph (figs. 7a–7b).	As severe or worse than standard photograph.
Vitreous hemorrhage	do	1a—present, but good quality photos possible; 1b—too much for photo, but can see well enough to classify ophthalmoscopically.	Too much to allow ophthalmoscopic classification.
History of vitreous hemorrhage.	None ever	1 or more in past, but none in past year.	1 or more occurring within past year: 2a—1 to 4 episodes; 2b—5 or more episodes in past year.

[1] It is recognized that some of these features may represent early proliferative disease, but common usage today places them in the nonproliferative phase.

Superficial microinfarcts ("soft exudates," "cotton-wool" exudates) (fig. 8) are to be counted in the total fundus. Less than five such lesions are "grade 1," and five or more qualify as "grade 2."

Venous dilatation has proven to be extremely difficult to classify even with good quality photographs and well-trained observers. For purposes of this classification emphasis has been placed on the degree of "sausaging" or "beading" of the veins. Sausaging or beading less than the standard (fig. 4) is graded 1; equal to or greater than the standard is classified grade 2. Venous dilatation alone, loop, ring or reduplication abnormalities without sausaging or beading are classified as grade 1.

"Intraretinal microvascular abnormalities" (fig. 5) is a term selected to designate the abnormal vascular structures within the retina variously interpreted as "shunt" vessels, dilated preexisting capillaries, fusiform aneurysms, or intraretinal neovascularization. Both the *numbers and size* of these vessels is considered, that is, the *area* of retina occupied by them.

Retinal edema is considered in the macular area alone and is graded by its geographic size; less than one disc area is considered grade 1, and a disc area or more is grade 2. This can only be studied accurately in stereo-photographs or on biomicroscopic examination, since the

retina frequently maintains normal transparency and edema can only be recognized by the increased thickness of the retina.

Fluorescein angiographic evaluation is to be done in the arteriovenous phase 15 to 25 seconds following the intravenous administration of 5 cubic centimeters of 10 percent fluorescein solution and again at 3 to 5 minutes postinjection. In the arteriovenous phase the intraretinal microvascular abnormalities and microaneurysms are to be compared with the standard (fig. 9) and if less, grade 1; if equal or greater, grade 2. The later 3 to 5 minute phase is used primarily to determine the degree of fluorescein leakage and is judged against figure 10 and graded appropriately.

The proliferative lesions are undoubtedly the most difficult to classify due to variations in location, extent, number, plane of proliferation, and degree of fibrous framework. It is recommended that these changes be graded according to specific descriptions rather than in comparison to standard photographs. However, illustrations of these lesions are included as examples (figs. 11 and 12). Nearly all proliferations are composed of two components, new-formed vessels and accompanying "fibrous tissue." Each of these elements is assessed and graded separately, although they are not independent. Early in their evolution new vessels usually appear "bare," (although, in fact, some transparent "fibrous" supporting tissue usually accompanies them). Later, visible white "fibrous" tissue appears adjacent to the vascular lumens and finally as new vessels "regress," the white "fibrous" tissue may predominate. Thus a fundus with grade 2 new vessels and grade 0 "fibrous" proliferation is probably in the early stage of proliferative retinopathy, while a fundus with grade 1 new vessels and grade 2 "fibrous" proliferation is in a late stage. Many early or moderately advanced cases of proliferative retinopathy will show new vessels only, without definite "fibrous" proliferations. Only very occasionally, however, are "fibrous" proliferations seen in the absence of any visible new vessels.

Neovascularization (new vessel growth with or without apparent fibrous supporting structure) is divided into that occurring on or within one disc diameter of the disc, and that occurring elsewhere in the fundus. A standard photograph is convenient in the former case and is used for evaluation of both neovascular and fibrous proliferation. As in the case of intraretinal microvascular abnoramlities, the *area* involved is judged. Elsewhere in the fundus (beyond one disc diameter from the nerve head) neovascularization is to be graded according to the number and extent of the lesions. Grade 1 is defined as four or fewer discrete patches of new vessels which occupy a total area of four

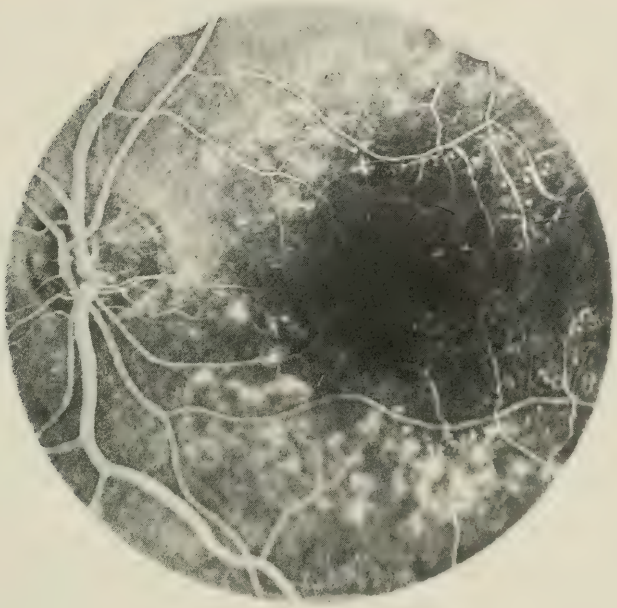

FIGURE 9.—*Standard photograph (fluorescein) arteriovenous phase—20 seconds—showing microaneurysms and intraretinal shunt vessels.*

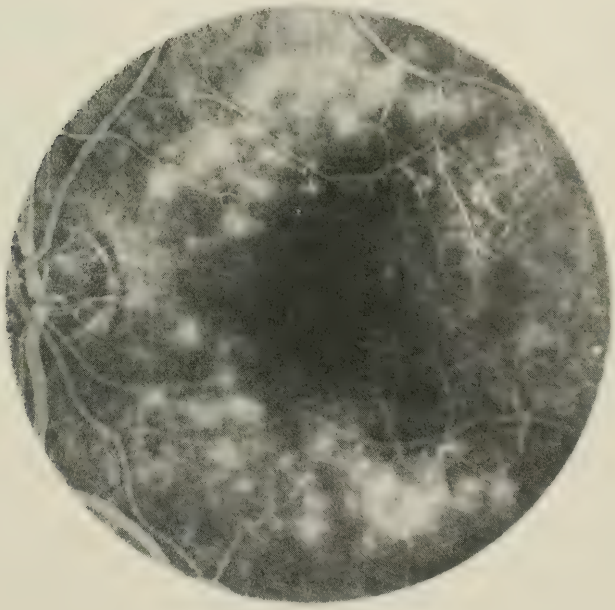

FIGURE 10.—*Standard photograph, 3 minutes—showing intraretinal leakage from abnormal vessels.*

disc diameters or less; grade 2 will be assigned when there are five or more discrete patches of new vessels or more than four disc areas of neovascularization.

Fibrous proliferative lesions, that is, semiopaque or opaque connective tissue growth with or without apparent vascularity, are graded in similar fashion according to location, extent and number.

"Plane of proliferation" refers to the elevation of proliferative lesions and is included as a measure of the contraction of the vitreous or of the fibrous proliferations which has occurred. Contraction of either vitreous or sheets of fibrous proliferation on the retinal surface leads to forward movement of the proliferations. If the proliferations are confined to the surface of the disc or retina grade 0 is assigned. If the proliferation is elevated from one-fourth to two disc diameters anterior to the plane of the *attached* retina, grade 1 is scored. If elevation is estimated to be two disc diameters or more anterior to the retina's normal position, grade 2 is assigned. Thus if proliferations are on the surface of *detached* retina, and the retina is elevated two disc diameters or more, the plane of proliferation is grade 2.

Retinal elevation due to separation, schisis, or "cyst" is defined by the area of the retina involved. Four or fewer disc areas in extent is grade 1, and five or greater is grade 2.

Large hemorrhagic lesions are divided into the preretinal type ("subhyaloid") and intravitreal. In the first instance, the hemorrhage in the patient's most severe 30° retinal area is compared to a standard (fig. 7a–7b) and classified as grade 1 if less extensive, and grade 2 if as extensive or worse than the standard. Intravitreal hemorrhage is further divided: 1a—Hemorrhage permits good quality photograph of fundus; 1b—Hemorrhage permits ophthalmoscopic classification of fundus but not clear enough for photograph; 2—Hemorrhage too extensive to permit ophthalmoscopic classification.

"History of vitreous hemorrhage," although obviously not a proper part of either an ophthalmoscopic or a photographic morphologic classification, is included to provide at least some measure of the "activity" of the retinopathy. This parameter is evaluated as follows: 1—History of one or more hemorrhages, but none in the past year; 2a—One to four hemorrhagic episodes in the past year; 2b—Five or more episodes in the past year.

Table II is the suggested form for recording the ophthalmoscopic classification of diabetic retinopathy as seen in the individual patient. At the time of examination each lesion is evaluated ophthalmoscopically according to the grading scheme outlined in table I and the grade is recorded in the appropriate space for each eye. Most examiners will

TABLE II.—*Form for recording ophthalmoscopic classification in individual patients*

Physician_____
Patient's name_____ Number_____
Date of birth_____ Date of examination_____

	Right eye	Left eye
A. NONPROLIFERATIVE		
Hemorrhages and/or microaneurysms		
"Hard exudates"		
"Soft exudates"		
Venous abnormalities		
Intraretinal microvascular abnormalities		
Retinal edema (at macula)		
B. FLUORESCEIN		
Arteriovenous phase (15 to 25 seconds)		
Late phase (3 to 5 minutes)		
C. PROLIFERATIVE		
Neovascularization within 1 disc diameter of disc		
Neovascularization, other areas of retina		
Fibrous proliferation within 1 disc diameter of disc		
Fibrous proliferation, other areas of retina		
Plane of proliferation		
Retinal elevation		
D. VITREOUS HEMORRHAGE		
Preretinal hemorrhage		
Vitreous hemorrhage		
History of vitreous hemorrhage		
E. OTHER OCULAR COMPLICATIONS		
Iris neovascularization		
Glaucoma		
Cataract		
Vein occlusion		
Arteriolar abnormalities [1]		
Optic atrophy		

[1] Localized irregularities of caliber, sheathing, and complete opacification of the vessel wall (white threads) are commonly seen in advanced diabetic retinopathy. The inferior temporal artery in fig. 11 exhibits all three features—narrowing to the right of the main patch of new vessels, sheathing to the left of this patch and "white threads" inferiorly. The committee on classification considered including a standard photograph for arteriolar abnormalities. However, since no agreement was reached, the authors have provided a place to describe the presence of these lesions.

prefer to classify the fluorescein changes photgraphically rather than ophthalmoscopically. A section for recording ocular complications not readily apparent in photographs but important in interpreting the function of the eye is included.

For purposes of collaborative studies it is essential that fundus photographs rather than ophthalmoscopic appearance be used for grading as many typs of lesions as possible. For this purpose certain photographic fields are suggested for standard use (fig. 1). These are chosen to assess the areas of the fundus most important for visual function and/or most commonly involved in diabetic retinopathy. Choice of the disc and macula need no explanation. Field 3, temporal to the macula, is chosen because of the frequency of involvement of this area early in diabetic retinopathy. Field 4 is chosen to provide a sample of the large retinal vessels and because it is a frequent site of neovascularization and fibrous proliferation. Field 5 is included for the same reason, but is slightly more difficult to photograph, requiring in many cases elevation of the patient's upper lid. Those lesions graded by comparison with standard photographs represent no problem and probably will be more accurately assessed when a photograph is compared with the photographic standard than when ophthalmoscopic appearance is compared with the standard. For lesions such as neovascularization and fibrous proliferation, i.e., retinopathic findings requiring evaluation of the entire fundus, the total number will be determined of each type of lesion present in all the available photographic fields of the eye to be classified. The written definitions in table I will then be utilized. Obviously, the greater number of photographic fields, the more closely the count will parallel the ophthalmoscopic grading. Standard areas 1 to 4 described in figure 1 represent the minimum and area 5 is recommended as a valuable supplement.

Table III represents the form for recording the photographic classification. Each of the patient's photographic fields is compared with the standard color photograph of the lesions listed and the grade recorded in the appropriate space. The mean of the individual fields is recorded in the "fundus as a whole" column. The same procedure is followed for fluorescein angiography, except that only field 2 is photographed at 20 sec. and 3 min. postinjection. In the case of "soft exudates," neovascularization in areas other than the disc, and fibrous proliferation, in areas other than the disc, the *number of lesions* in each field, excluding field 2 which is almost completely overlapped by contiguous fields, is written in the appropriate space and the grade of the fundus as a whole is derived by *adding* the lesions in each field and applying to the total the same definition used for ophthalmoscopic grading in table I. For grading macular edema and neovascu-

TABLE III.—*Form for recording photographic classification in individual patients*

Physician_____
Patient's name_____ Number_____
Date of birth_____ Date of examination_____

	Right eye						Left eye					
	Photographic field					Entire fundus	Photographic field					Entire fundus
	1	2	3	4	5		1	2	3	4	5	
A. NONPROLIFERATIVE												
Hemorrhages and/or microaneurysms												
"Hard exudates"												
"Soft exudates"												
Venous abnormalities												
Intraretinal microvascular abnormalities												
Retinal edema (at macula)	///		///	///	///		///		///	///	///	
B. FLUORESCEIN												
Arteriovenous phase (15 to 25 seconds)	///		///	///	///		///		///	///	///	
Late phase (3 to 5 minutes)	///		///	///	///		///		///	///	///	
C. PROLIFERATIVE												
Neovascularization within 1 disc diameter of disc		///	///	///	///			///	///	///	///	
Neovascularization, other areas of retina [1]												
Fibrous proliferation within 1 disc diameter of disc		///	///	///	///			///	///	///	///	
Fibrous proliferation, other areas of retina [1]												
Plane of proliferation												
Retinal elevation												
D. VITREOUS HEMORRHAGE												
Preretinal hemorrhage												
Vitreous hemorrhage												

[1] Exclude the disc and a zone 1 disc diameter wide around it.

larization and fibrous proliferation within one disc diameter of the nerve head, the single appropriate photographic field may be graded from table I (assuming in the case of macular edema that stereo photographs are available). The grade of that field then determines the grade for the fundus as a whole. Stereo photographs are also necessary for photographic evaluation of the "plane of proliferation."

Regarding the grading of vitreous hemorrhage, photographs alone are not completely suitable since gravitation of the hemorrhage into the inferior periphery will exclude it from the standard photographic fields and result in inaccurate assessment of this finding.

In order to provide the reader with examples of grading, the standard photographs (figs. 2–8) and eight additional fundus photographs (figs. 11–18) have been graded (table IV).

The committee recognizes that the classification does not have sufficient grades of each type of lesion to satisfy some investigators interested in a particular aspect of diabetic retinopathy. Grades 1 and 2 may be further subdivided to provide for particular needs, but any individual subdivision should attempt to utilize the basic major divisions indicated so that data will be comparable.

In addition to the morphologic classification outlined and discussed above, standardization of visual acuity recording and followup periods of observation are essential if data are to be comparable. It is recommended that visual acuity be subdivided as follows:

20/20 to 20/40—"good"
20/50 to 20/100—"moderate impairment"
20/200 to 5/200 or finger counting—"severe impairment"
5/200 or finger counting—"blind."

Followup observations should be recorded on an annual basis and grouped as follows: 1 year but less than 2 years; 2 years but less than 3 years; 3 years but less than 4 years; 4 years but less than 5 years; 5 years but less than 6 years, etc. The data should be reported at each yearly interval rather than combining all cases followed for more than a certain time and then calculating a mean followup.

It is hoped that general acceptance of these recommendations will result in the establishment of a central depository for collection of appropriate data at a university medical center under the auspices of the U.S. Public Health Service. This depository should perform the following functions: (1) Receive fundus photographs and objectively code the retinopathic lesions; (2) compare objective coding of fundus photographs with the coded ophthalmoscopic observations of the various investigators to establish the appropriateness of such a correlation and, if necessary, reeducate the investigators concerning use of the classification; (3) receive additional medical data (to be determined) on each patient under study so that these data, along with the fundus classification, can be coded, stored, and analyzed by appropriate computer techniques; (4) request and record followup information on each patient at designated periods; (5) continually analyze data concerning specific treatment techniques so that if and

TABLE IV.—*Examples of photographic grading*

Lesions	Figures															
	2	3	4	5	6	7A	7B	8	11	12	13	14	15	16	17	18
Hemorrhages and microaneurysms	2	1	1	1	1	1	1	1	1	[1] 1	2	2	2	1	1	1
"Hard exudates"	1	2	1	1	0	0	0	1	0	[2] 0	1	1	0	0	1	0
"Soft exudates" (number in field)	0	0	0	0	0	1	0	4	0	0	3	0	0	0	0	0
Venous abnormalities	0	0	2	0	0	0	0	0	1	0	1	1	1	1	2	0
Intraretinal microvascular abnormalities	[3] 0	0	2	2	[6] 0	1	1	1	1	0	1	1	2	2	2	[4] 1
Neovascularization within 1 disc diameter of the disc					2											2
Neovascularization other areas number of patches / disc areas	0	0	0	0		0	0	[5] 1 / <1	3 / 3	1 / <1	0	0	1 / <1	0	0	
Fibrous proliferation within 1 disc diameter of the disc					2											0
Fibrous proliferation other areas number of patches / disc areas	0	0	0	0		0	0	0	2 / <1	2 / 2	0	0	0	0	0	
Preretinal hemorrhages	0	0	0	0	0	2	2	0	1	0	0	0	0	2	0	0

[1] The punctate hemorrhages above the disc are actually in the vitreous (as judged in the stereo photograph). There is a single punctate retinal hemorrhage near the edge of the picture at 11 o'clock.

[2] The white spot near the edge of the picture at 9 o'clock is not an exudate, but an area of fibrous proliferation anterior to the retina, as was more clearly apparent in the stereo photograph.

[3] Upper left quadrant, to left of arteriole which leaves picture at 12:30 o'clock, is an area of questionable abnormality. Since it is questionable, it has been assigned Grade "0."

[4] Nasal to the disc (beneath the vein that leaves the picture at 2:30 o'clock) the abnormal small vessels are intraretinal. Elsewhere they are surface neovascularization.

[5] Without stereo, it is difficult to determine whether the abnormal vessels at the center of the picture are intraretinal microvascular abnormalities or new vessels on the surface of the retina. Actually in the stereo photo, it is apparent that *both* are present.

[6] Near the upper edge of the picture at 12 o'clock is a questionable area. Since it is questionable, Grade "0" has been assigned.

when a treatment becomes established as effective appropriate notification can be given.

In most chronic disease with a variable natural course, classification has been a stumbling block to communication among investigators. This has been particularly true in diabetic retinopathy. Lack of a generally acceptable classification and incomplete knowledge concerning the natural course of the disease has resulted in a multitude of therapeutic regimens, the efficiency of which is impossible to evaluate objectively. It is hoped that prospective studies will be undertaken utilizing this classification, and that eventually sufficient valid data will accrue to establish the effectiveness of various therapeutic measures advocated for diabetic retinopathy and clarify indications for their use.

It is anticipated that clinical investigators who wish to study diabetic retinopathy using the photographic classification proposed may be able to obtain a copy of the color transparencies at nominal cost from the University of Wisconsin Department of Ophthalmology (Dr. M. D. Davis). A sheet of instructions regarding use of the classification will accompany the transparencies.

ADDENDUM TO CLASSIFICATION OF DIABETIC RETINOPATHY

Some investigators may wish to use photographic standards for *all* parameters of the classification. Figures 8, 11 and 12 have been selected to allow their use for this purpose. Figure 8 serves as the standard for "soft exudates," Figure 11 for neovascularization in areas other than the disc and Figure 12 for fibrous proliferation in areas other than the disc. Photographic grading of retinal edema, plane of proliferation and retinal elevation can only be carried out from stereo photos and requires standard photos in stereo. In each case, the conventional definition for photographic grading holds true, that is, lesions as severe as or worse than the standard are Grade 2, giving prime consideration to the *area* of retina involved for all parameters except plane of proliferation and in this case judging the *distance* of the proliferations from the normal position of the retina. (M.D.D., F.L.M.)

References

1. O'Hare Classification (See p. XXI).
2. Lee, P. F. and others: A new classification of diabetic retinopathy. Am. J. Ophth. 62: 207–219, 1966.
3. Okun, E. and Cibis, P. A.: The role of photocoagulation in the therapy of proliferative diabetic retinopathy. Arch. Ophthal. 75: 337–352, March 1966.
4. Oakley, N. and others: Diabetic retinopathy I. The assessment of severity and progress by comparison with a set of standard fundus photographs. Diabetologia 3: 402–405, 1967.
5. Davis, M. D. and Myers, F. L.: Classification of Diabetic Retinopathy (Personal communication).

Discussion of Classification

WILLIAM BEETHAM, M.D., *and*
MATTHEW D. DAVIS, M.D., Moderators

Dr. Beetham: Every panelist here, I think, has a different classification of diabetic retinopathy. And, of course, I think I started out 40 years ago with the simplest classification, dividing it simply into the proliferative and nonproliferative type. I have taught and stuck with this until recently. Dr. Norton, would you comment more on this idea that we might come up with a new classification?

Dr. Norton: If you consider our preliminary Airlie House classification, you can see that we didn't make much headway over Dr. Beetham's classification of many years ago. All we have done is subdivide it. We have a background classification and a proliferative classification, and we have thrown in hemorrhage in addition.

We have tried in this classification to incorporate only the changes in the eye. There is no question that the ultimate classification will require other data. It is going to require data about the onset of diabetes and some indication of the control and the general medical status, and so on. I think another group will have to prepare that.

Representatives of the major classifications that are currently in the literature (from the Hammersmith group, from the Boston group, Dr. Okun, Dr. Davis, and others [1]) participated in the planning session, and have felt that they could work within the framework that is laid out in the preliminary Airlie House classification. I think, therefore, that we can get a classification that we all would agree with. We may not like it, because there are certain aspects that each one of us would prefer to see subdivided, but we all felt that we could keep within this broad framework so that our data could be compared with other workers.

Dr. Linfoot: I just have one comment about the O'Hare classification; namely, some of the areas were too broad.[2] There are situations

[1] EDITORS' NOTE.—A preliminary meeting on classification of diabetic retinopathy was held at the Airlie House prior to the first session of the symposium. Participants were: Drs. Davis, Fine, Glaser, Goldberg, Johnston, Kohner, McMeel, Myers, Norton, Oakley, Okun, and Wetzig. This preliminary classification was presented to the plenary session for the discussion which follows. A final form of the classification appears in chap. 2.

[2] O'Hare Classification, p. XXI.

that arise that make it very difficult with the O'Hare classification, to say: "Well, it isn't quite as severe as a '2,' but it really isn't a '1' either. I wonder about using a '1.5' category."

Dr. Davis: What Dr. Linfoot really is saying is that we need a more sensitive classification with more points in it. This, of course, is what the Hammersmith group has done with four photos for each parameter. They end up with a very sensitive system.

We don't suggest that the skeleton classification we are talking about is going to meet everyone's personal and detailed needs. We merely hope it will be a crossroad at which everyone's individual classification will meet, so that we can compare comparable things from group to group. I think everyone is going to want to have more detailed information on his own patients.

Dr. Thornfeldt: As far as the classification is concerned, I would like to suggest that the committee look at it as would a bunch of Republicans look at the Democrats' budget. The simpler we are, the better we are.

Dr. Oakley: In the Hammersmith classification we have five grades devised in terms of four photos. The photo is equal to the cutoff point between adjacent grades. If one wishes to have a sophisticated grading system for any single parameter, it is necessary to view a number of fields and either record them separately to give a realistic picture of the severity of the lesion over the retina, or to take a mean of several different fields in the way that is done in the Hammersmith classification. Looking only at the worst field, for example, is a purely artificial way of grading severity.

Dr. Roth: I am in favor of a montage effect of a number of photographs. I think one photo is totally inadequate. Three is a fair compromise. If you are going to take three, why not go up to eight or nine? It takes no more of my time for the ocular photographer to take nine photographs as compared to three. You can save the internist's time in grading these by keeping the number of classifications per photograph as simple as possible. I think you are not only going to save time, but you are going to come up with more meaningful data. You are going to get bogged down if you start going into five or six variations in your classifications per photograph.

Dr. Straatsma has been using a photographic montage effect with eight or nine photographs, and also has been attempting to project this while the patient is available in the office.

Dr. Joplin: I would like to discuss just two aspects of the proposed classification. First of all, the question of selection of the worst field: I think this is basically unsound as a means of describing the severity of retinopathy in an eye. If you adopt the worst field as the reference

field, then you will give exactly the same rating of severity to an eye that has only one field of involvement (and the rest of the eye normal) as you will give to an eye that is completely covered by retinopathy. The sample is the wrong sample, and it is an inadequate sample. I would suggest, from the experience we have had in grading many thousands of eyes for many, many years, that our standard analysis of three fields is quite rapid and certainly gives a representative sample. I would suggest, instead of a classification proposing the worst field, that you make it the mean of three specified fields.

Now as to the question of the number of standards that you might use in recording severity, you might think that it simplifies things only to have one standard and refer the severity of a component to that standard as better, equal, or worse. In actual fact, most of us are concerned with rating change as well as describing severity. For this reason it is, in fact, very much faster to allocate a change of an eye, over the course of time, as having crossed the cutoff point of one of several standards, rather than merely saying it is better, worse, or no change. I would therefore suggest that, to make your classification of practical value, you have three fields and that you have three or four standard photographs.

Dr. Spalter: I think sampling the retina is very much like the Gallup poll. Obviously the more areas of the retina we sample, the truer picture of the retinal pathology at any one time exists. We tried going out to the equator with about 25 fundus photographs. To make a montage of all that the fundus camera could see at one sitting took about 12 hours. This is obviously uneconomic and much too time consuming. However, one photograph is not an adequate sampling, and I agree with Dr. Joplin that we need a minimum of three preselected fields.

Dr. Davis: If we worked out a detailed classification with lots of grades, could we get you all to use it?

Dr. Joplin: There are 15 colleges in different parts of the world with our particular standards in use.

Dr. Okun: We have also attempted to utilize a classification system for many years in following patients' retinopathy, and have come to the conclusion that there really are different functions for the classification. One function is to compare what different people are starting with. That function worked very well, even with this very gross O'Hare classification. A second function is to explain in writing or by an analysis of tables the degree of progression of an individual case. This is where you need an extremely fine classification, and this is why we decided that initially a minimum of approximately nine fields be taken photographically. If in these nine fields the most severe area is not in-

cluded, then an additional field or two which shows the most severe area of involvement should be photographed. This, plus an entire fundus drawing, would give the picture that one starts with. When I am trying to determine whether or not a disease has progressed, I honestly find it extremely difficult unless I have fundus photographs to follow. Most progressions, regardless of how good your classification is, will occur right within the same classification heading, so, for the function of determining progress of disease, you really can't have enough classification grades. But for analysis from start to finish, over a long period of time, a relatively simple classification is then in order.

I don't think that anyone, every time he sees a patient, is going to take 15 sets of pictures and immediately try to determine what has happened with that patient. He will do it later on in comparison with other fundus photographs.

Dr. Fraser: I would like to talk to the general principle that has just been outlined, that we have first to decide what the classification is for. As you say, there are two functions. One is to record progress and the other is to assess the state at some point in time.

I would suggest that we could pick up one or two of the features in our classification as particularly important for assessing progress and the others as only necessary for assessing status to begin with. The ones for which you want to measure progress would have to be reversible features. Obviously, visual acuity is one.

The other consideration is sampling. This is terribly important. I would suggest we should try something that is a practical proposition in terms of work involved. To achieve this, we need more for the sampling than you have proposed.

Dr. Kohner: Dr. McMeel terms what we call the "irreversible eyeball" the very one which would be referred to an ophthalmologist for therapy, and he was quite upset that we wouldn't even consider these eyes. I think this new classification is an umbrella in order to accommodate everybody.

Dr. Davis: Visual acuity is going to be very, very helpful in judging results between different groups. We may have disagreement on what represents improvement otherwise. For instance, Mr. Dobree and I might say that when more fibrous tissue comes and the vessels get less, this is a natural event and is not an improvement. Perhaps everyone will agree with this. But the vessels going away is not necessarily going to be as universally accepted a criterion of a good result as maintenance of vision will be.

Dr. Peretz: It would seem to me that the location of the lesion affects visual acuity to a great extent. It can mislead you to check visual acuity. We all know a macular hemorrhage which settles inferiorly

will change visual acuity rapidly. Therefore, I would suggest that we photograph three areas, the first area being right around the macula, say within 10° or 15°, then going out concentrically to include the disk and the area from 15° to 30°, and the third photograph being in the far periphery. This way, if somebody says he has 20/40 and is getting better, and his vision is still 20/40, you know the disease process may have occurred out in the periphery. By the same token, you could have terrible disease encroaching on the macula but still sparing the macula. Somebody could say this eye is getting better, based on acuity, when, in fact, we all know it is getting worse.

Dr. Keen: Each time we see the patients in our double blind study, we take seven frames of each fundus (which are in a prearranged position set around the disc). When they are developed, we code them. We remove any information about the date on which they were taken and then, matching fields for each occasion, we try to arrange them so that the best is on the left and the worst is on the right. We can do this in relation to hemorrhages or other types of lesions. We then, having made our photo arrangement, record the order in which we have them. We break the code and see if there is any correlation between the order in which we put them and the date on which they were taken.

If there is true progression, either worsening or improvement, there should be a correlation. If there is no visible improvement, then there will be no correlation at all between the date and the order in which we put them. This can be done by the same person or by many persons very quickly. In this way one can tell statistically whether or not there is a change. The advantage, of course, is to get rid of individual bias. You are using the eye to grade itself. There is so much information in each photograph that two, five, or even 17 categories seem to me to be an offense in dealing with the information you have.

Dr. Kohner: I don't think this is, in any way, an objective method of assessment, because, if I put my mind to it, I could tell what the actual sequence of photos was, and put them into that order. By doing so, I might well be overriding the criterion of what was good or bad.

I would like to know how many people here actually have used photographic grading systems for eyes on large numbers of patients. If anybody has such experience, what documentation does he have for the validation of the method? It is absolutely vital that we should be able to validate the information that we are going to use. We cannot validate methods that depend on personal visualization of the patients. These cannot be validated unless you send the patient around from center to center. You cannot validate a method that depends on the individual photographer choosing what fields to photograph. You must have standard photographs taken of standard areas. These can

then be sent to different people, and can be validated by proving that different people will get the same results on the same set of photographs.

These are all points that we should consider, and any suggestion that cannot be validated and depends on subjective modification of the records by the person taking or making the assessment does not seem to be ideal for any purpose whatsoever.

Dr. Keen: We did try this method; our trial didn't work. We never put anybody back in the same grade.

Dr. Peretz: I wonder if introducing one more variable to the O'Hare symbols wouldn't help a great deal.[1] For example, on neovascularization the O'Hare system uses N_1 and N_2. I wonder if we should add a superscript indicating the area of retina involved (based on disc diameters). This would give us some idea of the extent of the neovascularization and the extent of the fibrous tissue proliferation and the extent of the preretinal hemorrhage.

Another symbol that I would think would be very helpful, even though this would not be objective, would be an impression on the part of the examiner to go with a parameter, be it neovascularization or fibrous tissue, which would indicate whether it was obviously getting better or worse in his estimation.

Dr. Norton: I don't know how we are possibly going to get something that we are all going to agree on if we make it more and more complex. For example, Dr. Joplin, I know you like the Hammersmith classification because that is what you have used. But it doesn't begin to cover the things that we can cover in this new classification. There are a lot of things that would have to be added to your classification, and you are not going to get away with 15 photos; you are going to have to add many more pictures than that. We arbitrarily decided to try to record three areas, just as the Hammersmith group did. If we want to classify all three pictures and then get a mean, that is fine. But if we can just get one picture classified, I would really be very happy. While it is easy to elaborate this classification and keep making it more and more extensive, the big problem to me is getting a standard in which we know that what is being treated by one ophthalmologist is the same thing that is being treated by a neurosurgeon, or by an internist with various drugs. I would be very happy to learn that much.

Dr. Duane: It seems to me we have come full cycle. I was confronted a long time ago with Drs. McMeel's and Field's complicated classification, and I was appalled when I saw what came out of O'Hare, because this didn't seem to add any great light, but it did add a whole

[1] O'Hare Classification, p. XXI.

lot of work to what we were already trying to do in coding our own information. I was delighted when I arrived here to see that you had really made a pretty minimal skeleton. Now, the Hammersmith people and the people in Atlanta or anywhere else can build on this, it seems to me, *ad infinitum*.

Semantically, it bothers me to talk about "background." I feel that this is the disease. Diabetes probably is a disease affecting the metabolism of the retinal tissue, expressing itself primarily in the vascular system. What happens in proliferation occurs, you might say, when the fire is almost over and the building is burned down. What we are concerned about is what goes on in these very early stages. That is the background; that is the diabetes.

I think there is a little too much emphasis on the fluorescein category. I think stereo examination of the retina and monochromatic green are important. We are finding almost as much with the green light as we are with fluorescein. It cuts right through overlying tissue, and gets down to the pigment epithelial layers. It shows us what is going on in a relatively simple way.

There seems to be a predilection, primarily among the nonophthalmologists, to put undue emphasis on vision. I would fully agree with what Dr. Peretz said. We all have seen patients who have what we consider relatively minor diabetic retinopathy but who have a hemorrhage right smack in the middle, and these people have poor vision. Now, if you do anything for these people, you might think that you have a wonderful result. But we know that these early forms wax and wane anyway. It doesn't make much difference what you do, because it will go away in most instances.

With regard to Dr. Kohner's remarks, we can hardly get through our own slides and you want to validate somebody else's. If you want a barrel of our slides, we will be glad to send them over to you. There comes a point of practicality when you just don't have any more time.

Dr. Kohner: After having used the O'Hare system, it took me one afternoon to classify my pictures.[1] To get my patients classified in the Hammersmith way took me about 6 weeks (ch. 1).

Dr. van Heuven: I agree that it is perhaps unrealistic to expect everyone to use a contact lens in a meaningful way to determine the architecture of the vitreous as it relates to the retina. But if we are going to classify "plane of proliferation," [2] I think we should recognize that there is a difference between the meaning of this in patients who have elevation at the disc and its meaning in patients who have elevation elsewhere. Elevation elsewhere may indeed and usually does

[1] O'Hare Classification, p. XXI.
[2] See ch. 2.

mean vitreous traction in the area of proliferation. At the disc you may very often have no vitreous detachment. Yet, elevation of the proliferation into the vitreous occurs. So when you have an elevation of proliferation away from the disc, I think it really means something, while at the disc it may not.

Dr. Davis: That is an excellent suggestion.

Dr. Beetham: I would like to see some mention in this classification of visual function or functional vision.

Dr. Davis: In this country, at least, 20/200 is legal blindness. We suggest that there would be two categories better than that; one would be 20/40 or better, one would be not as good as 20/40, but not as bad as 20/200.

Dr. Beetham: I want another category: 20/200 to 20/500.

Dr. Lundbaek: What is meant by "worse" and "better" may vary.[1] We found in our study that the greatest problem was in the classification of the proliferation. For example, what is the meaning of progressing from naked vessels to fibrous vessels. Is that good or is it bad? The naked vessels give you the danger of bleeding, and the fibrous vessels give you the danger of traction. We classify them separately, and say this is better as far as naked vessels are concerned (that they are less or do not appear as often); and this is better as far as fibrous tissue is concerned (that it does develop). But we cannot put them together and say they are better or worse.

Dr. Larsen: I think progress has been made since we have got the vitreous into this Airlie House classification. I agree it is very difficult to make a more subdivided classification than done here, because if you make it more classified, it's nearly impossible to compare the results. However, I would feel "proliferative retinopathy" [3] should be further divided. You use the term "retinal elevation," [3] and I should like to suggest this be grouped into retinoschisis and retinal detachment.

Otherwise, I find this classification fits with what we need.

Dr. Norton: I might comment, Hans, that we purposely used the word "retinal elevation" to avoid the problem of trying to differentiate between retinoschisis and retinal detachment.

We also thought we might have a subcategory listing complications, such as rubeosis iridis, glaucoma, cataracts, macular changes of a variety of sorts, and others. We thought we would exclude them as separate items because they are not an integral part of the retinopathy that we are trying to classify. We recognize that they are complications of the disease, but we thought they would just cloud the issue of classification.

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[1] See ch. 2.

Dr. Beetham: What compromises in the O'Hare classification do you feel were most unfortunate?

Dr. Davis: I think we ought to address ourselves mainly to the classification we have before us, because we all realize that the O'Hare classification should be a thing of the past.[2] It was designed for retrospective analysis. The most unfortunate part of the O'Hare classification was that we didn't consider anything except the proliferative features.

Dr. Kohner just asked me a question about our study (ch. 7). In our table I, where we talk about the H_2 category,[1] these were the eyes that had so much hemorrhage that they couldn't be classified. It looks as though they did very well. Sixty-three percent of them had as good vision or better at the end of the year. The reason for that is that they had very little vision to begin with, so they really couldn't get any worse.

The chief disadvantage of this sort of a classification is that it isn't made to follow the progress of any individual eye. If you look upon the O'Hare classification as a way to document or classify the progress of an individual eye, it's very bad. The groups are so broad, that an eye has to change a great deal in order to get from one group to another. But if you look upon it as a means of taking 50 patients from one center and taking another 50 from another center, where they were treated differently (and being sure that you are not comparing 50 bad prognosis patients with 50 good prognosis patients), I think the O'Hare classification has usefulness. And that was the reason we tried to formulate it.

Dr. Beetham: I have a question regarding classification from Dr. Spalter.[2] He says:

> A classification, of necessity, will also have a notation of visual acuity throughout the course of the patient's retinopathy. Therefore, should we not, in terms of life situations, avoiding purely scientific classification, note the visual acuity as functional for the patient's need or nonfunctional? That is, 20/400 may be functional for daily activities of the housewife but not for the truckdriver, and so on. This may more truly represent the goal of therapy regarding preservation of useful vision.

Well, that brings us to why we record visual acuity. It's a pretty useful thing. But I quote here from Dr. Davis. He says:

> The use of visual acuity as a magic criterion for judging results seems quite satisfactory.

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[1] O'Hare Classification, p. XXI.

[2] EDITORS NOTES.—Certain written questions from the floor were relayed to the panel by the moderators.

Then I have a quotation from Dr. Thornfeldt, who says:

> Visual acuity is extremely misleading, in that it is dependent upon so many factors, such as blood in the vitreous, and I believe this is not a valid means of expression.

I personally feel that the record of the visual acuity does not truly reflect the picture of retinopathy, and only pertains to a small area known as the foveal and parafoveal area of the retina. Undoubtedly, some such factor as functional and nonfunctional vision could be put into this classification without difficulty, I'm sure.

Dr. Norton: I am not opposed to a functional category, if somebody else wants to do it. What we really are trying to learn is the natural course of the disease and the influence of various therapeutic measures on this natural course. The fact that somebody is a housewife and may not need very much vision and that somebody else is an accountant and may need critical vision is of extreme importance to them as individuals. I hate to say it, but we are not interested in the individual at this point. We are interested in the overall disease and how to influence it. The only way we can do this is with fairly large numbers.

Dr. Davis: I don't think it's inconsistent to say that vision is a good criterion for comparing results between one center and another when we talk about groups of patients. I agree that it is a very poor criterion to document the course of an individual eye from time to time. It will be great if we can agree on a morphologic classification. We are going to have even more trouble using vision to compare groups of patients from center to center. But I certainly agree that when you want to characterize the state of an eye, visual acuity is surely not a complete way to do this.

Dr. Caird: Dr. Davis was suggesting that eyes rather than patients should be the units of measurement. I would strongly oppose this. Firstly, we are dealing with patients and not with two eyes. Secondly, the two eyes usually go together. If you take one eye, the second eye is just added on, and you multiply the prognosis in a way which is totally false. I would like to invert his argument about the patient whose one eye gets better and the other eye gets worse; he says he doesn't know how to classify the patient. I say the patient is just the same. Secondly, he was mentioning prognosis. The period of 1-year followup is very variable indeed, and this can be handled by the life table technique without any loss at all. It is extremely simple and extremely meaningful, and, if necessary, standard errors and rates for individual times can be given. I don't think this really ought to present any problem.

Dr. McMeel: In our data I think we have had three parameters that we have documented. One is a morphologic classification. The second is a classification of vision in each eye. The third is the vision

of the individual as a whole. You have three bits of information, and this can give a good overall picture; namely, the response of the disease process itself, the number of eyes, and then the best vision of the patient, which, in a sense, gives the functioning capacity. So why limit yourself to one classification?

Dr. Roth: I would like to add my vote to retaining visual acuity as an accurate measure in defining these patients. Of course, it does not tell us exactly what the retinopathy resembles. But visual acuity comes off relatively as a very accurate method of comparison between centers.

I was involved in a double blind study some years back, attempting to use fundus photography to compare groups. It is probably a part of my own lack of ability, but the two people involved in this study couldn't have been farther apart in statistical evaluation at the time, which left me somewhat pessimistic about this method. However, with finer photography, and with the stereoscopic element involved, I think there is still a great deal of hope in using fundus photography comparatively between centers. Fluorescein will certainly add to this. I begin to cringe a little when somebody begins mentioning counting certain things such as exudates or hemorrhages, because my experience has been that the failure to compare between centers comes about when classification becomes too complex and too involved. If you can keep the classification simple, I'm all for that, and results will be more valid.

As far as the mention of apparatus to help us in evaluation, we have had some recent discussions with the radiology people at UCLA concerning image intensification and counting devices, where virtually thousands of points can be counted in a very small area. This may offer hope in using an apparatus to grade a photograph more exactly.

Finally, I want to compliment the panel for meeting at O'Hare Airport when they named this classification, because it horrifies me as to what it might have been named had you met at Dulles Airport.

Dr. Oakley: May I just comment on the validation of methods of classification which has just been brought up by the last speaker? I think that any classification that we devise must be capable of being validated by the exhibition of photographs—to a variety of different and independent observers to make sure they achieve the same end classification. The advantage of photographs is that they can be sent around to numerous people. We have carried out this type of validation at Hammersmith with our photographic technique, and we find in the case of four of our five parameters, the exception being venous irregularities, that both our own staff as well as ophthalmologists at other centers can achieve an adequate accuracy and reproductibility with

respect to gradation of these four parameters into five grades. This depends on the use of good quality pictures when one attempts to do one's grading. This sometimes involves taking more than one photograph of a given area. One can't guarantee any single photograph will achieve the standard that is required.

There are also additional problems in the use of photographs. One is trying to grade eyes. And, in fact, we can only grade photographs. And we have problems in extrapolating grades of photographs to grades of eyes. We have discussed some of these in our submitted report to the meeting (ch. 1). We also come across problems in making meaningful serial observations when the very nature of some of the lesions, such as new vessels, is to come and go away again at different stages of proliferative retinopathy.

These are all points that must be considered very carefully by any body embarking on a system of classification, because they are points which, by bitter experience, we have run up against in the past, and which any other classification, based on photographs or on drawings or on direct observations of patients, will also encounter in the future.

Dr. Beetham: I have a question here: "In order to be comparable, the classification must be based on equivalent sensitivity of an examination. Would the panel define how and by what means the minimal examinations must be made in order to classify an eye?"

Dr. Norton: We spent a lot of time discussing this. One technique that would be easy to do is stereo fundus photography. These photographs could then be sent to any person who wanted to classify them. The individual who did the examination would not himself have to make the classification. There are disadvantages to this, because it requires covering as much of the fundus as possible. Then, somebody has to select out the worst areas for classification.

The other possibility includes individuals who are skilled at slit lamp examination of the fundus. Examination through the fundus camera may not be equivalent to slit lamp examination, but it would be very adequate. In addition, indirect ophthalmoscopy would be useful. We would feel these would be the minimum.

Dr. Beetham: Dr. Kohner, I have personally taken more than 10,000 colored fundus photographs. Yet, I feel utterly incapable of grading retinopathy by looking at them. And I take some pretty good pictures most of the time. Do you feel that photography is the best method of grading retinopathy or classifying retinopathy?

Dr. Kohner: Yes. There are various reasons for this. First of all, it is something that can be always checked by somebody else. Therefore, whatever I say about a photograph, other people can look at that photograph and agree with me or disagree with me.

The other reason is that it is a permanent record which can be looked at later. In verbal descriptions, we know that some people will point out more about some features than about others. At a later stage, you want to know about a feature which you perhaps wouldn't have noted when you did your first examination. Therefore, photographs are more useful.

It is best if the photographs have high quality, and we must look at the same area each time.

Dr. Beetham: Dr. Kohner, how many degrees of fundus do you get in your pictures? You don't get the fundus periphery at all, do you?

Dr. Kohner: We now photograph further out than we did previously. We now get pictures lateral to the macula, but we don't go as far as you would go with an indirect ophthalmoscope.

Dr. Beetham: How about the direct ophthalmoscope? You know, you're going to put an item in this classification that is going to stop some of us who don't know how to use the indirect ophthalmoscope—although I'm trying. With the direct ophthalmoscope you can get out very much further toward the periphery (and there is a lot of pathology there) than you can get with your fundus photograph. Is that not true?

Dr. Kohner: We take pictures of any area we think is of interest. We take standard fields, but, in addition, photograph any area which has a particular lesion we are interested in. I do agree that the quality of pictures gets less good, especially if you go lower down and further out. But you can still get pictures of those areas.

Dr. Patz: From a practical standpoint though, isn't most of the retinopathy near the posterior pole? Statistically, if you got out reasonably far toward the periphery, you would cover the larger percentage of lesions.

Dr. Beetham: I don't think you could get out that far with ordinary photography.

Somebody asked: "What was the reason the Airlie House classification includes 'plane of proliferation'?" [1]

Dr. Wetzig: This was a concession to Dr. Davis. Apparently, it was felt that once we saw proliferation, it was already a sign of vitreous detachment, which, of course, altered the prognosis. If the vitreous was detached without proliferation it was felt that there was a different prognosis than in the exudative type of disease.

Dr. Beetham: Dr. Spalter wants to know how you are going to classify fluorescein studies.

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[1] See ch. 2.

Dr. Norton: We are going to have a minimum classification on fluorescein, with the anticipation that those who are deeply interested in fluorescein will subdivide their own classification.

Dr. Peretz: We will want to treat more quickly those people who are getting worse rapidly. We have no way of seeing in this classification if they are getting worse or if they are stationary.

Dr. Norton: Walter, I think it just means you classify the patient each time you examine him. You are going to have to document the change either by recordings or in photographs, or, ideally, both.

Dr. Lundbaek: Wouldn't it be a better idea to have classification based upon the technique used for observation? For example, this preliminary classification is based mostly on photography, and it also includes fluorescein studies. Actually, we know that these two kinds of observations are quite different, and we don't know exactly what an observation with one technique means when we make the observation with the other technique. It is analogous to comparing light microscopy and electron microscopy.

This classification should also be useful in a situation where you want to observe with some kind of ophthalmoscope or with a slit lamp and a Hruby lens. A description or sketches or whatever could be done alone or in combination with photographs or fluorescein studies. It is well known that observations made with an ordinary hand ophthalmoscope are very different indeed. There again, it would be very necessary to distinguish observations made with the different kinds of apparatuses, especially from the ones you made with a strong ophthalmoscope.

So my suggestion is, somebody should try to make a taxonomy based on the instrument you are using, and should make one classification for each instrument.

Dr. van Heuven: I think Professor Lundbaek's statement is very good. I would like to stress the importance, when evaluating the state of the vitreous (which in this classification is under "plane of proliferation" as well as under "vitreous hemorrhage"),[1] that the best instruments available now are the slit lamp and the precorneal contact lens. I think many people may be tempted to do this entire classification on the basis of the indirect ophthalmoscope or the direct ophthalmoscope alone.

In our series we found a considerable number of patients who, with the indirect ophthalmoscope or direct ophthalmoscope, had no evidence of vitreous hemorrhage, for example, but who, with the better technique of contact lens and slit lamp, had quite a lot of vitreous hemorrhage.

[1] See ch. 2.

Dr. Okun: I would just like to say one word about how important an excellent classification really is. Because if one looks at a collection of raw data from several papers, such as has been presented by Dr. Davis in his review (ch. 9), and one takes all eyes with 20/40 visual acuity or better, this can represent all stages of proliferative retinopathy, including a grade 4, extremely advanced form which is advancing rapidly, which most people will agree has little chance of maintaining vision for another 3 months. In addition, it may include a patient who has very minimal proliferative retinopathy, and this patient, without any therapy, will do extremely well.

I would agree that it is very important to know the course of the retinopathy in a particular eye at the time therapy is undertaken, because those of us who have undertaken therapy usually reserve as one of our indications the rapid progression of the retinopathy in that eye, such that we think that that eye is ready for its demise. I have tried to use the O'Hare classification in comparing data of eyes treated and eyes not treated. Now, there is such a tremendous leeway between N_1 and N_2 and also within N_2 and beyond, whatever that might be, that you can run into all kinds of difficulties trying to tell what is happening. The only thing that you can tell from this classification is a general idea of what we are starting with.

The most interesting thing to me is to see the number of patients with background retinopathy who have been treated by many means. From the statistics of Dr. Caird and others, we know that background retinopathy really has a very excellent prognosis compared to the proliferative type.

Dr. Beetham: Dr. Okun, nobody agrees with you more thoroughly than I.

PART II

Natural History and Visual Prognosis

CHAPTER 3

Diabetic Retinopathy as a Cause of Visual Impairment

FRANCIS I. CAIRD, D.M., M.R.C.P.

The present paper reviews the prognosis for vision in diabetic retinopathy on the basis of the findings of Caird and Garrett (*1*) (1963), Caird (*2*) (1965) and Caird, Burditt and Draper (*3*) (1968), and the epidemiology of diabetic blindness on the basis of the data of Sorsby (*4*) (1966).

PROGNOSIS FOR VISION

Table 1 shows the chances of visual deterioration in 5 years found in 135 diabetics with "background" retinopathy (O'Hare classification [1]) and initial good vision, that is, a visual acuity of 6/12 or better in both eyes (*3*). It will be seen that in younger patients the chance of blindness (visual acuity less than 6/60 in both eyes) is only 3 percent in 5 years, and in patients over 60 at diagnosis of diabetes, 20 percent. It is likely that chances of a similar order run for 10 years. The chances of visual impairment or blindness, that is, of visual deterioration sufficient to give rise to difficulty with employment, rise with age from 3 percent in those under 30 at diagnosis of diabetes to 32 percent in those over 60. A similar trend is apparent in the data of Appelmans, van Hoonacker, and Daels (*5*). The risk of visual impairment is substantially greater when there are retinal hemorrhages or exudates than when microaneurysms only are present. The presence of visual symptoms is a further prognostic factor, since it was found (*1*) that the chances of blindness were three to five times greater in eyes with visual impairment than in those with good vision. Better control of diabetes does not improve prognosis (*1*).

In "background" retinopathy, therefore, prognosis for vision is good over periods of several years, though increasing age at diagnosis of diabetes, severer degrees of retinopathy and the presence of visual symptoms all carry a worse prognosis. In general, treatment of "background" retinopathy designed to improve prognosis for vision will need to be very efficient indeed.

Department of Geriatric Medicine, University of Glasgow, Stobhill General Hospital, Glasgow, N. 1, Scotland.

[1] O'Hare Classification, p. XXI.

TABLE 1.—*Prognosis for vision in 15 diabetics with background retinopathy and initial good vision (visual acutity 6/12 or better in both eyes) (3)*

Age at diagnosis of diabetes	Final vision	5- year chances percent		
		Severity of retinopathy		
		All grades	Microaneurysms only	Hemorrhages and/or exudates
0–29	Imparied or blind	3	0	4
	Blind	3		
30–59	Impaired or blind	14	12	21
	Blind	3		
60+	Impaired or blind	32		
	Blind	20		

Imparied vision: visual acuity 6/18 to 6/60 in the better eye.
Blind: visual acuity less than 6/60 in the better eye.

The chances of visual deterioration in proliferative retinopathy are of the order of ten times or more greater, as Table 2 illustrates. In 5 years, 30 to 40 percent of younger and 40 to 60 percent of older patients are blind, the proportions with "economic" blindness being 40 to 45 percent and 70 percent. An effect of age is again demonstrable. The small differences between the chances of "legal" and "economic" blindness are taken to indicate that in proliferative retinopathy, unlike "background" retinopathy, visual deterioration is likely to be severe rather than moderate, while the small differences between the prognosis in patients who had proliferative changes when first seen and those in whom they were observed to develop suggest that, again in contrast to "background" retinopathy, there is no long period of low risk to vision when proliferative changes begin.

The figures in Table 2 are similar to those of Deckert, Simonsen, and Poulsen (*7*). They also found that prognosis was worse when pro-

TABLE 2.—*Prognosis for vision in diabetics with proliferative retinopathy and initial good vision (2, 6)*

Proliferative retinopathy	Onset of diabetes	Blindness	Percentage chance of blindness after years—		
			2	5	10
Present at first observation	Growth	Economic	15	44	71
		Legal	14	43	67
	Maturity	Economic	29	70	100
		Legal	20	61	83
Observed to develop	Growth	Economic	21	44	
		Legal	13	32	
	Maturity	Economic	39	71	
		Legal	20	43	

Growth onset diabetes: onset before age 20.
Maturity onset diabetes: onset after age 20.
Blindness—economic: visual acuity less than 6/15 in the better eye.
Blindness—legal: visual acuity less than 6/60 in the better eye.
Economic blindness thus includes legal blindness.

liferative changes were present near the disc, and where there was persistent proteinuria, but did not find it worse when visual symptoms were present (Deckert, personal communication). This is a further difference from "background" retinopathy.

Table 3 shows the prognosis after vitreous hemmorhage (*3*). Four years after the first such hemorrhage only one-third have vision better than 6/12 in the better eye, but this proportion is little less than that after 1 year. This suggests that if blindness does not occur in a year it is unlikely to do so in the next few years; perhaps a stable state is reached.

The implications of these findings for the treatment of proliferative retinopathy would seem to be as follows: If treatment is to be effective it will need to be applied soon after proliferative changes develop, and perhaps before they produce symptoms; this implies the need for regular examination of patients known to have "background" changes to detect the earliest manifestations of a more serious situation. Any treatment even if given to essentially asymptomatic patients must result in preservation of vision in at least 60 percent of younger patients after 5 years before any benefit can be deduced. Even after 10 years about 20 percent of patients with proliferative retinopathy are not legally blind.

EPIDEMIOLOGY OF DIABETIC BLINDNESS

Nearly 700 diabetics were registered as blind each year between 1955 and 1962 in England and Wales (*4*) (Table 4). Ninety-two percent were over 50 and nearly half were over 70 years of age. Diabetic retinopathy was the cause of 7 percent of all new blind registrations and of as many as 20 percent in middle-aged women. From these data age- and sex-specific incidence rates can be calculated; these rise steadily with age, and are approximately 50 times greater over the age of 70 than under the age of 30. They are greater in women than men at all ages over 50. It is also possible to calculate from the age structure of the known diabetic population found in the Birmingham survey (*8*) that the risk of blindness from retinopathy in diabetics is 11 times that

TABLE 3.—*Prognosis for vision after 1st vitreous hemorrhage (3)*

Duration of followup (average)	1 year	4 years
Number of patients	39	22
Visual acuity in better eye (percent):		
6/12 or better	33	32
6/18 to 6/60	36	27
Less than 6/60	31	41

TABLE 4.—*New blind registrations from diabetic retinopathy in England and Wales, 1955–62 (4)*

	Age					All ages
	15–29	30–49	50–59	60–69	70+	
Number of new registrations each year (average):						
Men	3	28	26	48	48	153
Women	2	18	60	188	250	518
Total	5	46	86	236	298	671
Percentage of new registrations:						
Men	4	11	10	9	2	4.4
Women	4	10	19	21	5	8.6
New registrations per 100,000 per year:						
Men	0.10	0.64	1.32	3.03	4.65	0.87
Women	0.16	0.37	2.21	8.97	13.6	0.61

from all causes in the general population (Table 5). In middle age this excess risk is almost 30 times. The cumulative risk of blindness in diabetics of different ages at diagnosis of diabetes and different durations of diabetes can also be determined. The figures given in Table 6 have a rather wide range owing to differences in methods of calculation, but even after 30 years of diabetes in young patients the risk of blindness is not over 7 percent, a proportion very similar to the 8 and 9 percent found by Lundbaek (*9*) and White (*10*) in their young diabetics with diabetes of 20 to 30 years' duration.

Sorsby (*4*) found no evidence of any increase in the incidence of blindness due to diabetic retinopathy in England and Wales between 1955 and 1962, but since 1962 there has been a 50 percent increase in registrations under the age of 60 (Ministry of Health, personal communication). Unfortunately, no data are available on registrations over the age of 60. There is no reason to think that this increase is likely to be due to change in registration habits, since the benefits derived from registration have not altered in the period in question, and there has been no general increase in registrations.

Further information is provided by a study of the registered blind in the city of Oxford (population 109,000). Of the 193 blind, the cause

TABLE 5.—*Absolute and relative risks of blindness due to retinopathy*

	Population	Cause of blindness	Age				All ages
			15–29	30–49	50–69	70+	
Incidence per 100,000 per year.	General	All causes	3	3	17	150	19
	Diabetic	Retinopathy	[1] 20	83	212	367	204
Relative risk	Diabetic	Retinopathy	[1] 7	28	13	2	11

Relative risk: Risk of blindness from diabetic retinopathy relative to that for all causes in the general population.

[1] Approximate.

TABLE 6.—*Estimated cumulative risk of blindness in relation to duration of diabetes*

Age at diagnosis of diabetes	Percentage risk of blindness at age—					
	30	40	50	60	70	80
20	0.1–0.2	1.0–2.5	1.6–6.3			
40			0.8	2.9–3.8	5.0–7.1	
60					1.8–2.1	5.5–5.7
General population	0.09	0.12	0.15	0.32	0.49	1.99

Methods of calculation: From prevalence of retinopathy at Radcliffe Infirmary Diabetic Clinic and risks of blindness from retinopathy.
General population: From Sorsby (*4*).

was diabetic retinopathy alone in 13 (7 percent), and retinopathy together with other causes in a further five (*11*). The prevalence of blindness due to retinopathy alone is thus 12 per 100,000; the comparable figure for the United States was 16.5 in 1957 (*12*). From these figures the following calculations can be made: 1.9 percent of diabetics are blind from retinopathy and 2.7 percent from all causes; 5.1 percent of diabetics with retinopathy are blind; the proportion of diabetics blind from all causes is 13 times that in the general population.

Sorsby (*4*) does not record data for the incidence of blindness due to ocular complications of diabetes other than retinopathy. In younger blind diabetics blindness is due to proliferative changes in at least 80 percent (*13*). In older patients the proportion due to exudative changes is probably greater.

These epidemiological studies show that in England and Wales diabetic retinopathy is the cause of less than 10 percent of all blindness, though there is evidence of a recent increase in incidence. The great majority of the diabetic blind are over 50, and nearly half are over 70. A diabetic is between 10 and 15 times as likely to become blind from retinopathy as a nondiabetic from all causes of blindness, but at any one time only 5 percent of diabetics with retinopathy are blind.

ACKNOWLEDGMENTS

I am grateful to "Diabetes" and the American Diabetes Association for permission to reproduce data in Tables 1 and 3 and to Messrs. Blackwells Scientific Publications Limited for Tables 2, 4 and 5.

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CHAPTER 4

Clinical Observations Concerning the Pathogenesis of Diabetic Retinopathy

MATTHEW D. DAVIS, M.D.
FRANK L. MYERS, M.D.
RONALD L. ENGERMAN, Ph. D.
GUILLERMO DE VENECIA, M.D.
YVONNE L. MAGLI, B.S.

In 1961 we began a long-term study of the natural course of diabetic retinopathy. Our methods of examination, details of which have been previously reported, (*1,2*) have included binocular indirect ophthalmoscopy, stereoscopic fundus photography and slit lamp biomicroscopy with flat contact lens in all suitable cases. Fluorescein angiography has been done in selected patients. During the years 1961 through 1966, 320 patients were examined. Of these, 165 have been followed at intervals of 1 to 12 months for 1 year or more and 71 for 3 years or more. The patients available to us have been chiefly those with visual symptoms or with ophthalmoscopic findings striking enough to lead to their referral. Consequently approximately two-thirds of our patients have shown neovascular and/or fibrous proliferation of some degree.

The clinical course of diabetic retinopathy which we have observed is most easily viewed as the result of a gradually increasing ischemia, due presumably to a progressive narrowing and/or obliteration of capillaries or terminal arterioles. This interpretation allows orderly explanation of all of our clinical observations and is consistent with our own histopathologic findings and the majority of previously published studies.

Most histopathologic studies are in agreement that the characteristic microaneurysms and hypertrophic capillaries of diabetic retinopathy occur adjacent to acellular presumably obliterated capillaries (figs. 1 and 2). There is disagreement however in regard to the sequence of these changes. Cogan and coworkers (*3*) favor their "shunt hypothesis," which suggests that the initial change is a loss of capillary

From the Department of Surgery (Ophthalmology), University of Wisconsin Medical School, Madison, Wis.

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pericytes ("mural cells"), to which a contractile vasomotor function is ascribed, resulting in dilatation of some capillaries, preemption of blood flow by them and secondary atrophy and obliteration of adjacent vascular channels. We and other investigators (*4,5*) feel that the sequence of events is opposite to that proposed in the "shunt hypothesis," the capillary obliteration occurring first with secondary dilatation and hypertrophy of adjacent vascular channels which must now accommodate a greater flow of blood. In our experience, the "shunt vessels" seem histologically too infrequent to account for the majority of aneurysms and hypocellular or atrophic capillaries.

The pathogenesis of the microaneurysm has been the subject of a great deal of speculation. (*3*) We are inclined to agree with Wise (*6*) that this lesion probably represents an abortive attempt at neovascularization. While it is possible that the immediate stimulus for the formation of both microaneurysms and new vessels is tissue hypoxia, as suggested by Wise, other metabolic changes or alterations in the composition or flow of blood may be more important. Unfortunately, neither histopathologic study of random postmortem material nor present clinical examining techniques are entirely satisfactory for investigation of the initial events in the course of diabetic retinopathy. Study of experimentally induced diabetic retinopathy in animals appears to be the most promising approach to this problem and merits increased attention. Clinically, further refinement of and experience with fluorescein angiography promises to provide another valuable tool for research in this area, as does correlation of clinical and histopathologic findings in individual eyes.

At any rate, in those patients in whom we have been able to follow the evolution of diabetic retinopathy from what appears ophthalmoscopically to be an early stage, a gradually increasing ischemia could logically explain the typical sequence of events observed over its entire course.

Diabetic retinopathy begins ophthalmoscopically with the appearance of a few red dots representing microaneurysms and deep punctate retinal hemorrhages (figs. 3, 8a). These appear first in the posterior retina, particularly in the region temporal to the macula (fig. 4). Although they frequently are in haphazard arrangement, at times the aneurysms are seen bordering an area of very faint soft exudate, an ophthalmoscopic picture reminiscent of the histologic finding of microaneurysms surrounding an area of capillary obliteration (fig. 5).

As diabetic retinopathy progresses, a stage is reached in which soft "exudates" become common. Although at times as prominent as the cotton wool patches of vascular hypertension (fig. 6), soft exudates occurring in diabetic retinopathy are usually less white, less opaque

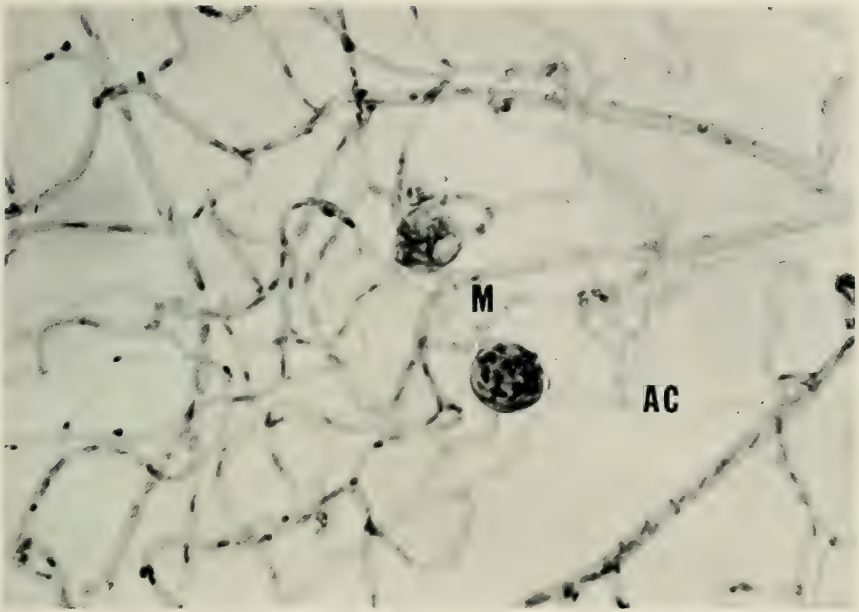

FIGURE 1.—*Microaneurysms (M) adjacent to area of acellular capillaries (AC). Trypsin digest specimen diabetic human retina. PAS and Hemotoxylin stain.*

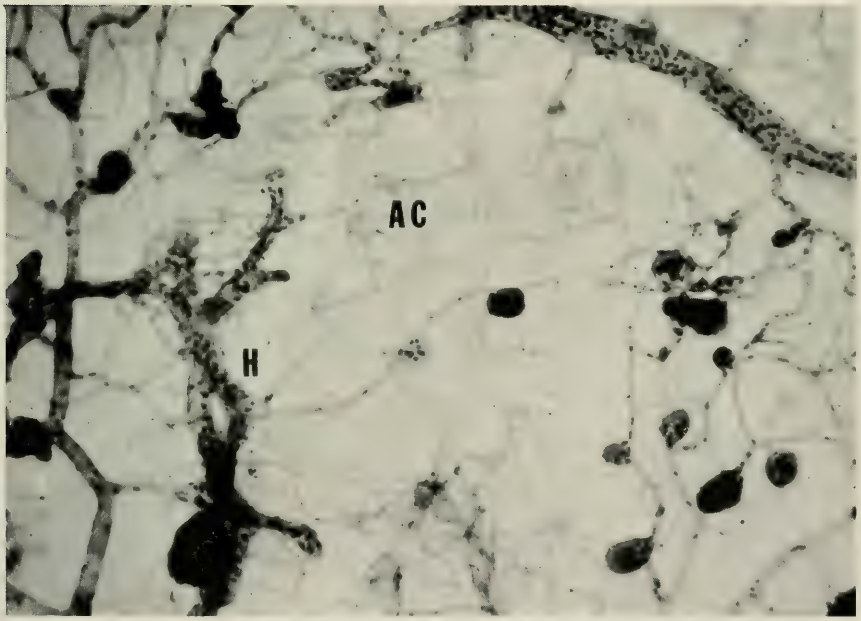

FIGURE 2.—*Microaneurysms and hypertrophic hypercellular capillaries (H) surrounding region of acellular capillaries (AC). Trypsin digest specimen diabetic human retina. PAS and Hematoxylin stain.*

FIGURE 3.—*56-year-old male diagnosed as diabetic at age 40. Early diabetic retinopathy with 3 red dots below and temporal to the macula of the right eye, probably all representing microaneurysms.*

FIGURE 4.—*Common site of early changes of diabetic retinopathy temporal to the macula. The left eye of a 46-year-old man whose diabetes was diagnosed at age 33 on routine physical exam. Hemorrhages, microaneurysms and hard exudate.*

FIGURE 5.—*Microaneurysms surrounding faint soft exudate (arrow). Lower nasal quadrant of left eye of 21-year-old man. Diabetes diagnosed at age 15. Older brother has severe proliferative retinopathy.*

FIGURE 6.—*Prominent soft exudates with surrounding microaneurysms. Left eye of 42-year-old man. Diabetes diagnosed at age 34. BP 120/75.*

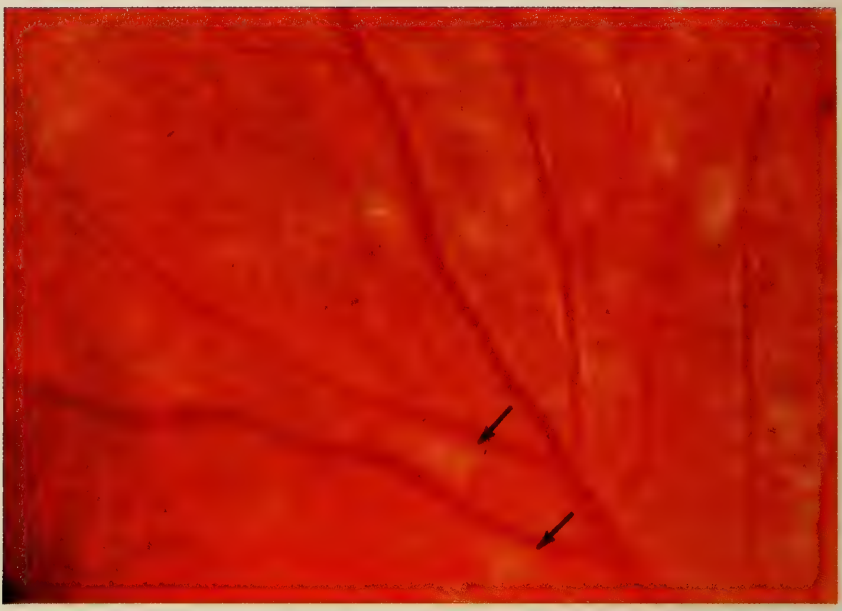

FIGURE 7.—*Progression of retinopathy in a 36-year-old man. Diabetes diagnosed at age 23. Left eye, superior nasal quadrant.*
7A.—*January 1964. Multiple faint soft exudates (arrows).*

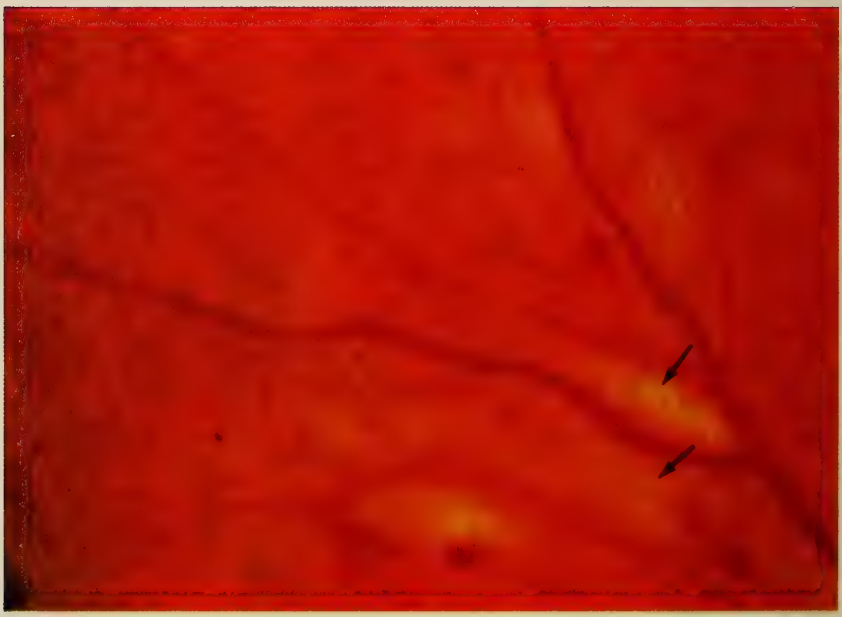

FIGURE 7B.—*August 1965. Soft exudates more prominent (arrows).*

FIGURE 7C.—*November 1965. Venous beading has begun.*

FIGURE 7D.—*December 1965. Increased venous beading. Some small arterioles appear as white threads (arrow).*

FIGURE 7E.—*February 1966. Soft exudates gone.*

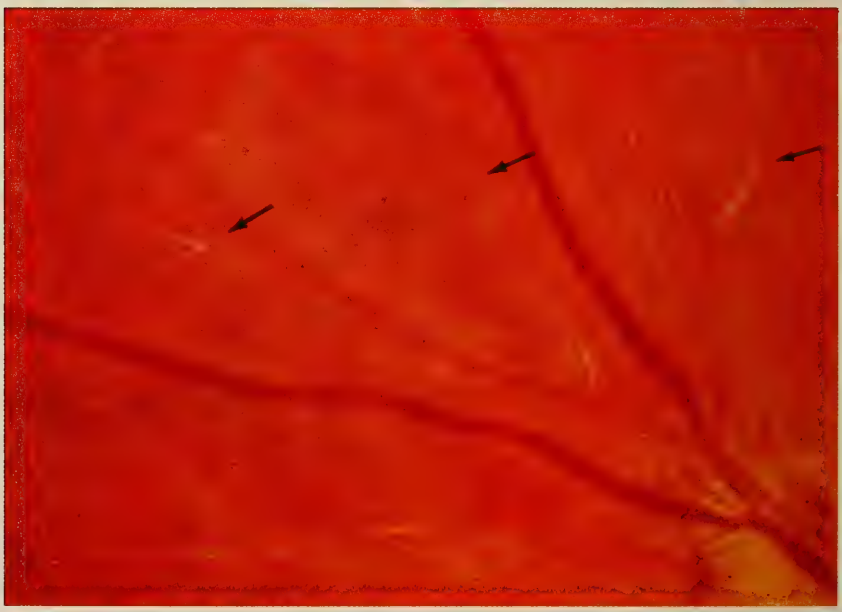

FIGURE 7F.—*May 1966. Beading less. More arteriolar branches appearing as white threads (arrows).*

FIGURE 8.—*Progression of retinopathy. Same eye as Fig. 7. Superior temporal quadrant.*

8A.—*January 1964. Scattered microaneurysms and/or punctate hemorrhages of early retinopathy. Vessels normal.*

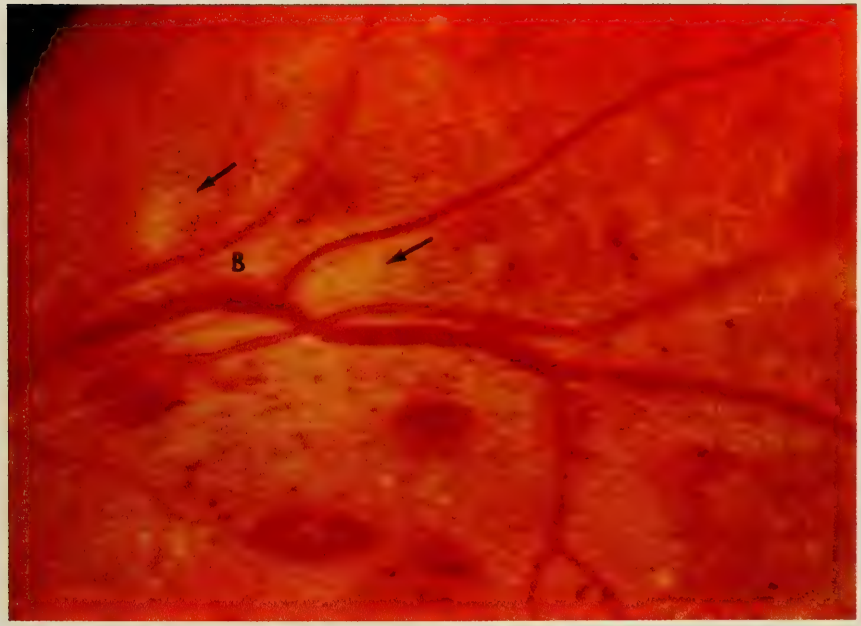

FIGURE 8B.—*October 1965. Blot hemorrhages, faint soft exudates (arrows) and early segmental venous dilitation (B).*

FIGURE 8C.—*November 1965. Venous beading, intraretinal "shunt vessels" (arrows).*

FIGURE 8D.—*December 1965. Marked venous beading. New prominent soft exudate (arrow). Early neovascularization (NV).*

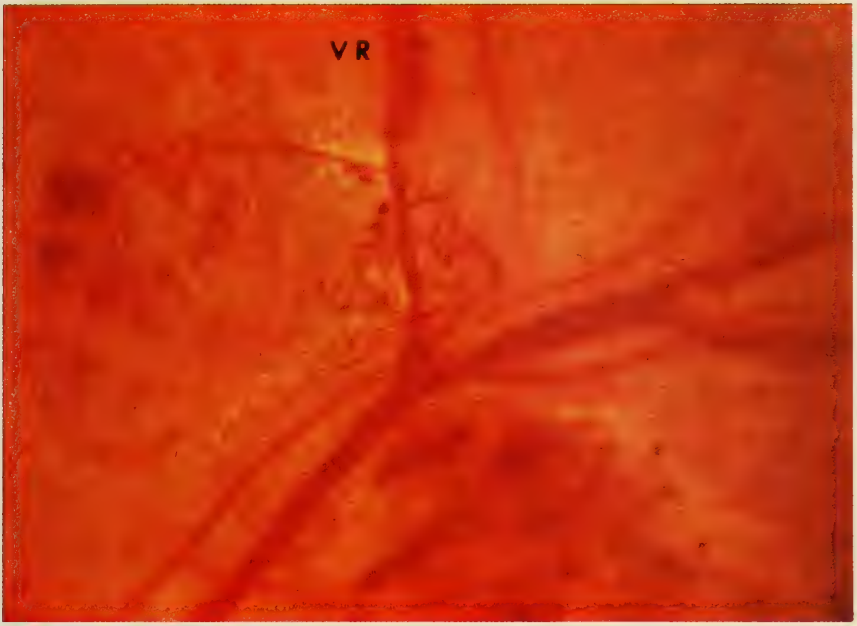

FIGURE 8E.—*February 1966. Soft exudates faded, venous reduplication (VR).*

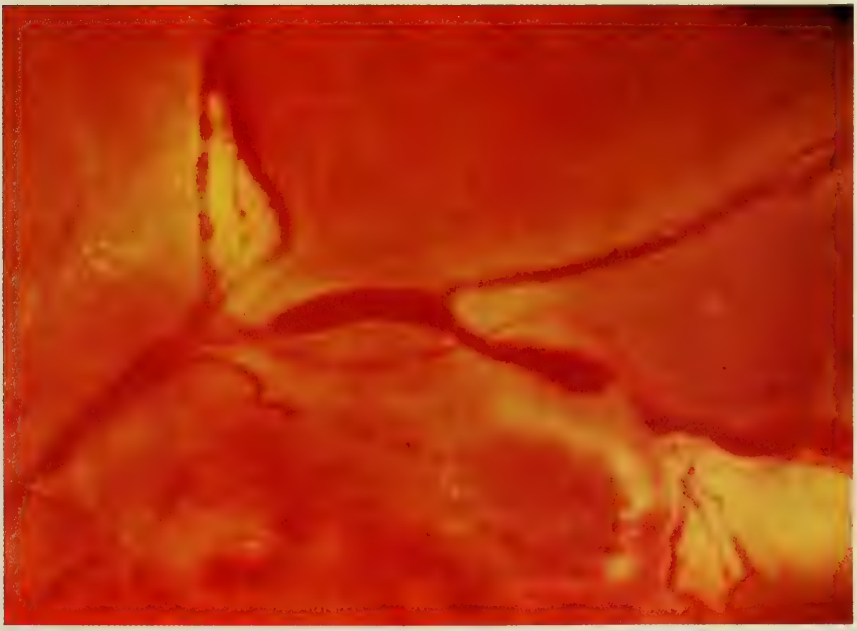

FIGURE 8F.—*May 1966. Marked venous changes, retinal edema and subretinal exudate.*

FIGURE 9.—*Progression of retinopathy in a 27-year-old man. Diabetes diagnosed at age 8. Left eye, superior temporal quadrant.*

9A.—*December 1964. Early venous beading, scattered retinal hemorrhages and microaneurysms.*

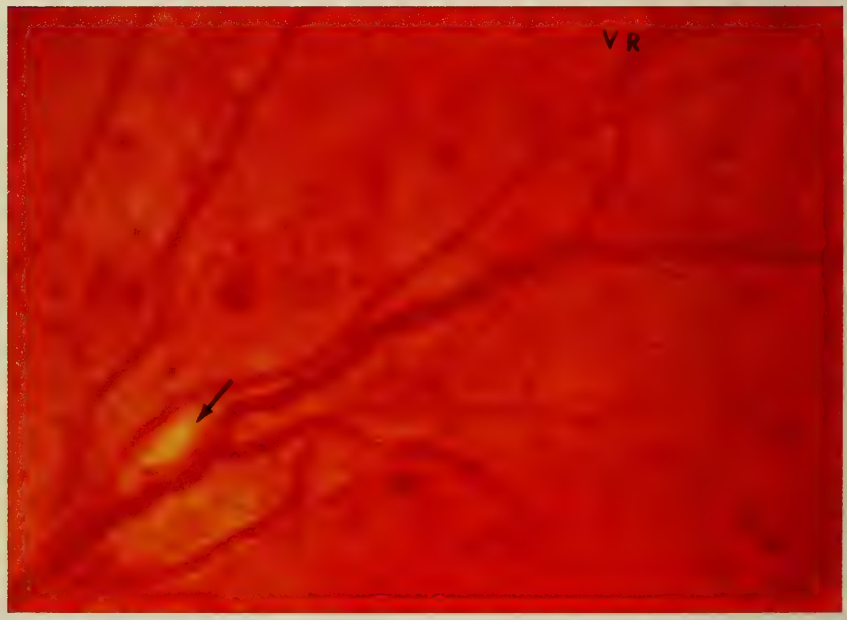

FIGURE 9B.—*August 1965. Venous reduplication (VR), soft exudate (arrow).*

FIGURE 9C.—*October 1965. Soft exudate gone, more venous beading and reduplication.*

FIGURE 9D.—*April 1966. More venous beading and reduplication.*

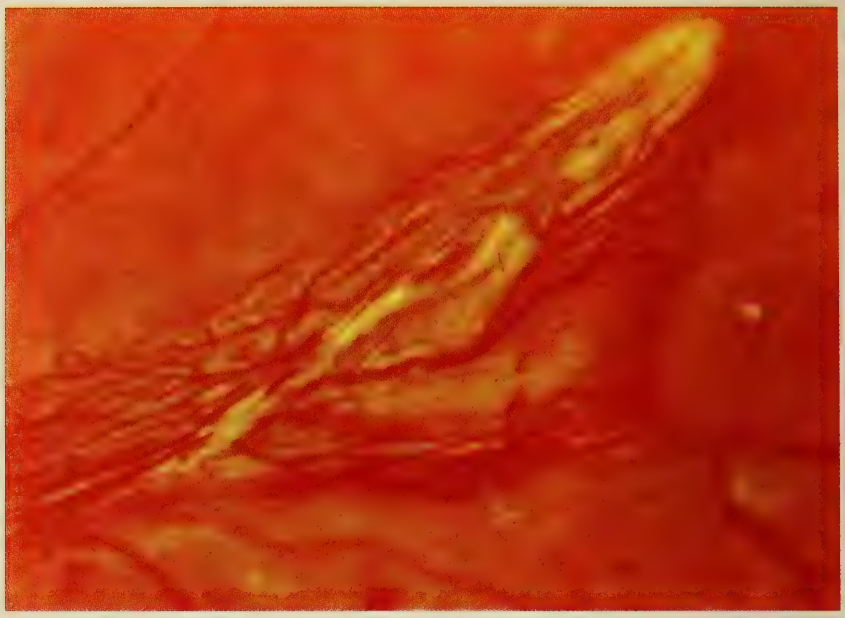

FIGURE 9E.—*July 1966. Marked preretinal neovascularization arising from area of venous beading.*

FIGURE 9F.—*September 1966. Fibrous proliferation, regression of neovascularization, hemorrhage between attached retina and detached vitreous obscures retina.*

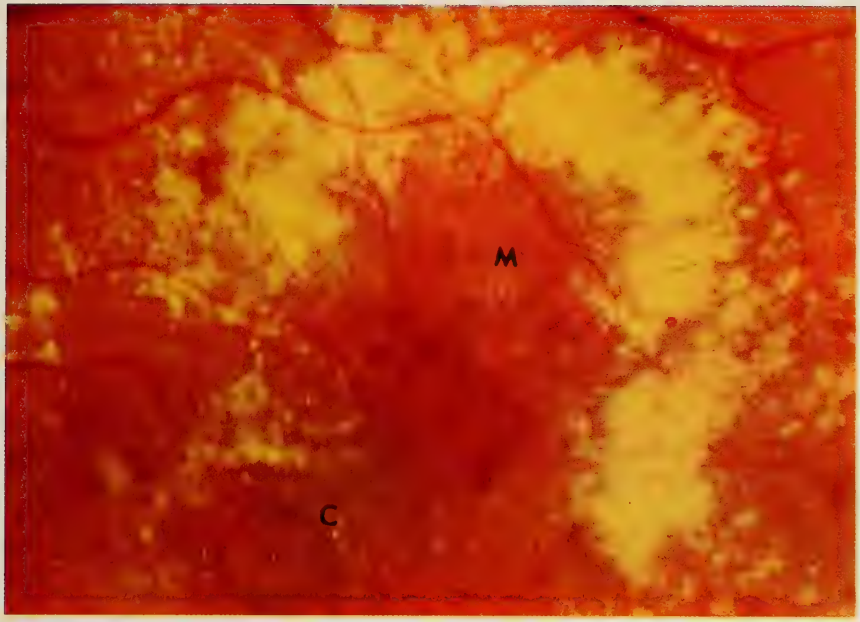

FIGURE 10.—*53-year-old adult onset diabetic. Thick walled microaneurysms (M) in left eye above and temporal to the fovea. In stereophotograph, thickening (edema) of retina around the microaneurysms was apparent. A ring of hard exudate surrounds the edematous area. Cyst is present at fovea (C).*

FIGURE 11.—*Right eye of 29-year-old juvenile onset diabetic. Neovascularization originating from the optic disc.*

FIGURE 12.—*New vessels originating from the superior temporal vein of a 20-year-old juvenile onset diabetic.*

and may be easily overlooked (figs. 5, 7a). They are most conspicuous at a time when microaneurysms and retinal hemorrhages are moderately severe and venous dilatation is beginning, but usually fade shortly after the onset of neovascularization (figs. 8d–8e). The excellent study of Esmann and coworkers (*7*) in which the incidence of hard and soft exudates was compared among diabetic patients of various ages and durations of diabetes demonstrates that soft exudates are as typical of diabetic retinopathy as are hard exudates, and is in agreement with our impression gained from serial observations that these lesions occur relatively early in the course of diabetic retinopathy and then tend to disappear. There is now general agreement that the cotton wool patches of vascular hypertension represent ischemic infarcts in the nerve fiber layer due to occlusion of terminal arterioles. There seems little doubt that a similar mechanism is active in diabetic retinopathy, perhaps with less complete and more gradual arteriolar or capillary closure.

Another characteristic feature of diabetic retinopathy, venous dilatation and irregularity, frequently becomes prominent concurrently with soft exudates or shortly after their disappearance (figs. 7, 8). Many observers have commented on the similarity of venous changes in diabetic retinopathy to those of central retinal vein or branch vein occlusion, and have hypothesized that partial venous occlusion or increased blood viscosity or coagulability might be of significance in the etiology of diabetic retinopathy. Actually the similarity between venous changes in venous occlusion and diabetic retinopathy is not so great as might appear on casual observation. The segmental venous dilatation ("beading") characteristic of diabetic retinopathy is not a prominent feature in venous occlusion, and is not usually accompanied by the widespread retinal hemorrhages along the peripheral branches of the involved veins which are so typically seen with venous occlusion. Perhaps an even more important difference is the frequent presence of visible granular blood flow within severely dilated veins in diabetic retinopathy, a finding characteristic of partial obstruction of blood flow upstream from the point of observation. Venous changes similar to those characteristic of diabetic retinopathy are seen in retinopathy due to arterial insufficiency as seen in pulseless disease (*8*, *9*) and carotid insufficiency (*10*). It seems clear, therefore, that the venous changes of diabetic retinopathy also may be logically attributed to ischemia secondary to partial obstruction in capillaries or arterioles. The true nature of the dilated venous segments ("beads") is uncertain, but their close spatial and temporal relationship to venous loop formation and neovascularization on the surface of the retina (figs. 8, 9) strongly suggests that they represent a type of vasoproliferation. Our

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histopathologic observations in the single classical case available to us for clinical histopathologic correlation are consistent with this explanation.

Early in the course of diabetic retinopathy the arterioles generally appear normal. Later an increase in light reflex is common but only in the late stages does opacification of the vessel wall occur, producing the appearance of sheathing or completely obscuring the blood column (fig. 7f). This process usually begins in the smallest visible branches and may spread gradually up the arterial tree. It characteristically occurs concurrently with visible granular blood flow in the corresponding veins. Although this ophthalmoscopic evidence of arteriolar involvement in diabetic retinopathy occurs only late in its course, it is not unreasonable to postulate that similar more subtle, perhaps functional, changes begin at the onset of diabetic retinopathy in capillaries and/or arterioles too small for ophthalmoscopic visualization. Histopathologic changes have not been described in the arterioles in the earliest stage of diabetic retinopathy, but Ashton (*4, 11*) has demonstrated hyaline construction of terminal arterioles when retinopathy was fully established.

Two other lesions characteristic of diabetic retinopathy, hard exudate and retinal edema, may also be logically related to ischemia, since both presumably result from abnormal permeability of microaneurysms and other abnormal vascular channels which are themselves, in our opinion, the result of ischemia. This increased permeability is shared also by new vessels on the anterior surface of the retina or in the vitreous cavity, and by new formed vessels generally. Retinal edema occurs characteristically adjacent to microaneurysms, with the edematous zone in turn surrounded by hard exudates (fig. 10).

Of all the manifestations of diabetic retinopathy, neovascularization is perhaps the most readily attributable to ischemia of a critical degree or involving an area of retina of critical size. The appearance of neovascularization midway in the evolution of diabetic retinopathy is consistent with such a view, as is its frequent regression in late stages when severe sclerotic changes in retinal arterioles and visible blood flow in retinal veins indicate severe vascular insufficiency, presumably leading to ischemia too severe to stimulate (or support) vasoproliferation. Neovascularization begins most commonly on the optic disc or along one or more of the major retinal veins (figs. 11, 12). The new vessels at first appear "bare," but later are accompanied by fibrous or glial tissue which is initially thin and semitransparent. The later more opaque appearance of these fibrous proliferations is frequently due to a shift in their position away from the retina, leading to the same loss of transparency as occurs in the sensory retina when it becomes

detached from the pigment epithelium. At other times there appears to be true thickening of this fibrovascular tissue. Following the appearance of fibrous tissue, the new vessels themselves frequently decrease in size and number. This "regression" of new vessels may be easily misinterpreted as "improvement" due either to therapy or to the natural course of the retinopathy. Actually it is frequently during such "regression" that preretinal and vitreous hemorrhage from the new vessels begins. It is of utmost importance to emphasize that the unfavorable prognostic implications of preretinal new vessels result not only from their role in the production of vitreous hemorrhage but equally or more importantly from the vitreoretinal adhesions resulting from them.

The final characteristic of diabetic retinopathy requiring discussion is vitreous contraction. Its role in the course of proliferative diabetic retinopathy has been discussed previously in detail (*1*), and it is necessary here only to emphasize its importance in the production of both vitreous hemorrhage and retinal detachment. So long as vitreous contraction has not occurred, the new vessels and fibrous tissue proliferate in a two dimensional sheet along the internal surface of the retina, only rarely extending forward into the vitreous cavity. Firm adhesions characteristically form between the fibrovascular proliferations and the vitreous framework. When the vitreous contracts, the new vessels are pulled forward and they in turn exert forward traction on the retina at their sites of origin, frequently leading to retinal detachment. Traction on these thin-walled fragile new vessels also seems to be an important cause of vitreous hemorrhage.

The excessive permeability of the new vessels demonstrated by fluorescein angiography has led to the suggestion that the vessels themselves might damage the viteous and lead to vitreous contraction (*2*). The recent work of Kloti (*11*), who observed posterior vitreous detachment following experimental embolization of multiple small posterior branches of the central retinal artery in owl monkeys, suggests that ischemia per se may cause vitreous contraction, and provides one more argument in support of ischemia as the underlying mechanism in diabetic retinopathy.

Our conviction that ischemia plays a fundamental role in the pathogenesis of diabetic retinopathy stems not so much from the sum of the observations outlined above, but rather from the ability of this single concept to provide a unifying theme for all the characteristic manisfestations of this disorder. We have been impressed that the proliferative phase of diabetic retinopathy blends almost impercetibly with the preproliferative phase, and this too is consistent with the "ischemia hy-

pothesis". If our interpretations are correct, all of diabetic retinopathy is fundamentally "proliferative."

What therapeutic possibilities are suggested by the foregoing discussion? If capillary or arteriolar narrowing is the initial lesion and begins long before the first opthalmoscopic evidence of diabetic retinopathy, treatment should ideally be aimed at preventing or minimizing this change. Perhaps careful control of the diabetes early in its course does this. More thorough understanding of the fundamental metabolic defects in diabetes may offer other approaches to the problem in the future. In the patient who already has ophthalmoscopically visible diabetic retinopathy, the "ischemia hypothesis" dictates that retinal blood flow is already reduced to a critical level, at least in some areas. Theoretically, we might consider as therapeutic possibilities either an improvement of blood flow or further reduction of flow to a point beyond the critical level for stimulation of vasoproliferation but still sufficient for preservation of some retinal function. If part of the reduction of blood flow is functional, rather than structural, we might hope to improve it. Does pituitary ablation perhaps produce its effect by increasing retinal blood flow? If so, and if gradual progression of ischemia continues from the new improved "baseline" following ablation, resumption of progression of the retinopathy some years after what appears initially to be a favorable response would be easily explained. On the other hand, pituitary ablation might, theoretically, produce its beneficial effect by reducing retinal blood flow.

In the case of photocoagulation, several therapeutic mechanisms are possible. If areas of ischemia of critical degree are destroyed, they could no longer stimulate vasoproliferation. It is even conceivable that destruction of such areas might improve blood flow in neighboring areas. Other less speculative mechanisms of action of photocoagulation are obvious. Destruction of a path of new vessels eliminates a potential or actual source of vitreous hemorrhage and prevents extension of the vitreoretinal adhesions associated with it. The chorioretinal adhesions produced may in some cases help to slow the progress or limit the area of subsequent retinal detachment. Another possible mechanism may be the prevention of the later fibrotic stage of neovascularization, a stage when vitreous hemorrhage frequently begins, perhaps because of contraction in this fibrous tissue. Another intriguing possibility is that photocoagulation prior to the development of preretinal neovascularization might induce vitreous contraction before vitreoretinal adhesions have formed. This might protect the eye if neovascularization subsequently developed.

The preceding discussion is based on clinical impressions resulting from careful serial observations (particularly stereoscopic fundus

photography and slit lamp biomicroscopy with flat contact lens.) Statistical data concerning so variable a condition as diabetic retinopathy is not easy to compile or analyze, but we shall present a preliminary statistical report, using the abbreviated classification devised for this conference (ch. 7).

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CHAPTER 5

Evolution of Lesions in Proliferative Diabetic Retinopathy: An 8 Year Photographic Survey

JOHN H. DOBREE, M.D., F.R.C.S.

Eight years ago a study of proliferative diabetic retinopathy (P.D.R.) was undertaken with the main object to determine the chronological sequence of the lesions; the main research tool has been the fundus camera, and each eye under study is being photographed at regular intervals. The first 3 years' findings on 15 patients have already been reported (*1*). Subsequently, a further 43 patients have been added to the series, and the study has been extended with a view to identifying the pathological changes taking place in the retina and vitreous; in these observations the fundus contact lens has been used to augment the ophthalmoscope and fundus photographic appearances. Some of these findings, especially those dealing with condensations on the posterior vitreous face and the formation of retino-vitreal bands, have been reported (*2*, *3*). The data relating to all lesions recorded (photographically unless otherwise stated) in the whole 8-year period are now presented.

Clinical Material

A total of 112 eyes from 58 patients are included in this review. The time of observation varies from 9 months to 8½ years. In over half the cases it has been over 3½ years. In 17 patients (34 eyes) observations have extended for over 5 years. The interval between examinations is usually 3 to 4 months.

In 70 eyes which include all the earlier cases, no treatment has been given. In the remaining 42, the chronological changes have been modified by light coagulation, but the changes prior to treatment and indeed following treatment provide additional data.

Primary and Secondary Changes in P.D.R.

By "primary changes" is meant the cycle of events in the fundamental lesion of P.D.R., namely the growth and later regression of the new

St. Bartholomew's Hospital, London.

vessels themselves. By "secondary changes" is meant the changes in the disc, retina, vitreous and choroid, caused either by hemorrhage or connective tissue formation in the intraocular tissues.

THE PRIMARY (NEW-VESSEL) CHANGES

It was found that new-vessels evolve in 3 stages (*1*).

Stage I.—An initial "naked" stage of vessels with extremely fine walls and without ophthalmoscopic evidence of supporting connective tissue. These "naked" vessels appear either on the disc or as isolated areas on the retina. After some 1 to 4 years this stage passes on to stage II:

Stage II.—In this period there is a considerable increase in the size of the new-vessel systems, both disc and retinal, and a condensation of connective tissue gradually forms around them. This connective tissue condensation appears to be part of the primary change and is not necessarily preceded by hemorrhage, although if the latter occurs, connective tissue changes are even more marked. Stage II marks the most florid stage of the new vascular formations and in 1 to 2 years merges into stage III:

Stage III.—The stage of regression or cicatrization. In this stage the new-vessel formations in the disc area regress and the connective tissue forms relatively avascular masses of connective tissue overlying the disc. The retinal groups of new vessels are replaced by flat sheets of avascular cicatricial tissue. At the same time there is an attenuation of the vessels of the normal retinal system.

Further Observations on Primary Lesions

It is unnecessary to recapitulate previously published data on the sites, form or evolution of these three stages of the primary lesions; the original observations have been confirmed as the series has been extended. Certain additional findings have, however, been made which may be significant; they are as follows:

The sites of origin of the new vessels

There are three sites of election for new vessels in P.D.R.; namely, on the disc, along the course of the main vessels from 1 to 3 disc diameters from the disc and roughly in the equatorial region. In the first two named sites, the larger vascular formations are more commonly found; the more equatorial lesions are usually smaller. This poses a query as to the nature of the stimulus causing the new vessels. If the trigger mechanism is anoxia, why are the main formations so

often at these particular sites? One feature in common is the crossing or coming together of the large vessels. Are some of the new formations anastomotic vessels? There is a close similarity between these new vessels and those occurring after retinal vein occlusion.

The relative proportions of eyes having new vessels on the disc

This problem arose in the selection of lesions for light coagulation, this particular group being regarded as unsuitable.

The 112 eyes were examined to study this point; 57 of these (50.9 percent) had disc vessels, but some of the remaining 49.1 percent which have had no disc lesions so far may well develop them later (*3*).

SECONDARY CHANGES IN P.D.R. (Table I)

The changes secondary to the new-vessel formations which have been recorded photographically in the series are as follows:

(*a*) Subhyaloid, vitreous and choroidal hemorrhages
(*b*) Vitreous retraction
(*c*) Thickening of the posterior vitreous face
(*d*) Formation of retinovitreal bands
(*e*) Traction on retinal vessels
(*f*) Retinoschisis
(*g*) Flat holes and retinal detachment
(*h*) Late choroidoretinal changes
(*i*) Pathological arterioles
(*j*) Rubeosis iris and secondary glaucoma

Again these lesions have been previously described, but several further observations are added.

Hemorrhages

Subhyaloid hemorrhages are believed to be of considerable importance because of their relationship to vitreous retraction. They were found in 24 out of 112 eyes (22.5 percent).

In the early stages the hemorrhage lies directly over or a little below the bleeding vessel. Later it gravitates to a lower level. If a vitreous retraction is present the lower boundary of the retrovitreal space is demarcated by an irregular line of blood or, in some cases, by a "swallow's nest" hemorrhage with a convex lower border and a horizontal upper limit (*4, 5*). As the pocket of blood is localized, the presence of even a large subhyaloid hemorrhage may cause no symptoms.

Vitreous hemorrhages.—Nineteen patients in the series have

TABLE I.—*Secondary changes in 112 eyes with P.D.R.*

Lesion	Number times found	Percent incidence
(*a*) Hemorrhages:		
(i) Subhyaloid	24	22.5
(ii) Vitreous	93	83.0
(iii) Choroidal	6	5.6
(*b*) Vitreous retraction (in 28 eyes)	22	78.8
(*c*) Thickenings of posterior vitreous face	16	14.3
(*d*) Retinovitreal bands	33	29.3
(*e*) Traction lines at retinovitreal interface	4	3.6
Traction on retinal vessels:		
Retinal	7	6.3
Disc	10	8.9
(*f*) Retinoschisis	7	6.3
(*g*) Flat holes	3	2.7
Retinal detachment	12	10.6
(*h*) Late choroidoretinal changes	8	7.1
(*i*) Pathological arterioles	19	17.9
(*j*) Rubeosis with glaucoma	10	8.9

not had a vitreous hemorrhage sufficient in degree to cause symptoms. One male aged 29, first diagnosed as having P.D.R. 8 years ago, has not had a single hemorrhage in either eye. A female aged 35 had no hemorrhage in either eye for 4 years, although multiple stage I lesions were present. The remaining 93 patients (83.0 percent of cases) have all had vitreous hemorrhages, often multiple, and occurring most usually in the late stage I or stage II in the new-vessel development.

Choroidal hemorrhages were found in six of the 112 eyes (5.6 percent). In one eye the effusion was massive and caused a complete choroidal detachment. These cases support the view that the choroid plays an occult role in P.D.R.

Vitreous retraction (Fundus contact lens examination)

This has been found so frequently since the observations of Davis (*6*) and Tolentino et al. (*7*) that it is now regarded as the usual state of affairs in any but the earliest cases. It was present in 22 out of the 28 cases for which it was examined (78.8 percent). It varies from a barely perceptible chink to a complete retraction of the vitreous. It occurs most frequently temporal to the disc, especially over the posterior pole. This may be due to the fact that there is a particularly firm adhesion of the vitreous face at the disc margins. (Corroborative evidence of this attachment is the fact that a subhyaloid hemorrhage will sometimes track around the lower margin of the disc rather than encroach over its surface.) The mechanism of the vitreous retraction is obscure. Some instances are clearly secondary to large subhyaloid hemorrhages; in others it is postulated that plasma escaping from the new vessels behind the vitreous face gradually pushes it forward (*2*).

Thickening of the posterior vitreous face

This secondary change present in 16 of the 112 eyes (14.3 percent) is a major cause of large avascular sheets or bands forming in the late stages. It is always associated with vitreous retraction. Thickening of the posterior vitreous face where the vitreous is in contact with a large subhyaloid hemorrhage commences a week or so after the hemorrhage and initially appears as a greyish film, rather like the bloom on a plum. Often before the hemorrhage absorbs, its color is obscured by this vitreous thickening.

Retinovitreal bands

These were found in 33 eyes (29.3 percent of cases). Like the vitreous face bands, these are essentially avascular but they originate in an entirely different manner. Both retinal and vitreous tissue appear to take part in their formation. They originate in lines of traction between two fixed points, the disc and a focus of stage III vessels in the retina commonly form such foci; in this case a scimitar-shaped band is formed arching from the disc often along the course of the main vessels where new-vessel formations are common. The concave side of the scimitar band is usually toward the macula but the base is firmly adherent to the internal limiting membrane which is sometimes drawn toward the cavity of the globe forming a localized retinoschisis (*2*). Similar retinovitreal bands may run between any two areas of cicatrization of stage III retinal vessels. A wrinkling of the retinovitreal interface, seen ophthalmoscopically as parallel darker and lighter lines, is occasionally found radiating across the posterior pole in these cases (present in four eyes, 3.6 percent). In one eye the macula was displaced.

Traction on retinal vessels

Seven cases (6.3 percent) in this series have been noted. These have always been found associated with vitreous retraction. It is known that the vitreous is often adherent to the retina over the adventitia of the retinal vessels (*8*); when the former retracts, the vessel, (a vein in all cases) was plucked bodily out of the retina carrying with it strands of that tissue. This kinking has been suggested by Davis (*9*) to be conducive to retinal vein thrombosis and hemorrhage, and this is certainly our view. A surgical division of the vitreous band is required but this must await better techniques than at present available.

Traction displacement of large trunks on the disc caused by contracture of primary vessels in stage III has also been noted in 10 cases (8.9 percent).

Retinoschisis

This is a comparatively common occurrence in the later stages of P.D.R. but has received little attention. In this series it was found involving an area of one-eighth to one-half of the retina in seven cases. It usually starts in the equatorial area possibly at the site of a subhyaloid hemorrhage from a group of new vessels with resulting vitreous traction. Several cases have been watched for years while the condition has slowly progressed. So far surgical treatment has been unsatisfactory.

A more localized form is also occasionally seen running along the course of a retinovitreal band.

Flat holes and retinal detachments

In three cases small round holes some one-fourth of a disc diameter in extent and not associated with subretinal fluid have been found. In one, situated some three disc diameters nasal to the disc, a vitreous band forming on the posterior surface of a vitreous detachment was clearly responsible. In the second, about three disc diameters from the disc above the superior temporal branches, the operculum was initially in contact with the retina but was gradually torn away and carried forward by the retracting posterior vitreous face and eventually came to be several millimeters in front of the hole. The third case is a macular hole in which the posterior vitreous face is in contact with the lower margin of the hole but elsewhere has retracted to form a chinklike retrovitreal space. The role of vitreous retraction in the production of these three holes is clear.

Twelve cases of complete retinal detachment have been observed in in this series, but there are probably other examples in eyes with opaque media in which the fundi could not be seen. Of these 12 cases, eight were thought to be clearly related to traction on the retina by connective tissue bands, in two there was a previous retinoschisis, and in the other two no precise cause could be found. It is worth noting that the first two cases of holes without subretinal fluid did well following light coagulation; this was not carried out on the third (the case with macular hole). In all retinal detachment cases but one, surgery has been unsuccessful; and in that, relapse followed 1 year after an encircling operation.

Late choroido-retinal changes

Babel and Rilliet (*10*), Fischer (*11*), Beetham (*12*), and others have drawn attention to the not inconsiderable numbers of eyes which after several years pass into a quiescent stage marked by a regression

of the new-formed vascular systems and a freedom from hemorrhages. These eyes may retain a greater or lesser degree of vision for an indefinite period. Eight of such eyes, one treated and seven untreated, have been observed. All eight eyes were advanced stage III cases and had, in addition to the regression of the new vessels and a condensation of connective tissue in their vicinity, the following features in common which seem to be partly retinal and partly choroidal in origin:

(1) Visual acuity in the order of 3/60 to 6/36.

(2) A marked attenuation of the vessels of the normal retinal tree.

(3) A general pallor of the fundus especially at the posterior pole. This is apparently caused by an atrophy of the choriocapillaris. The larger choroidal vessels are seen here and there and among them irregular fibrotic areas. This forms a background to a widespread patchy pigment disturbance often with pigment aggregates at the macula itself. A fine greyish film overlies the whole area; this may represent glial changes in the internal limiting or the nerve fiber layer (fig. 1).

It seems almost certain that both retina and choroid are involved in these changes.

Pathological arterioles

Ashton (*13*), using an India ink injection and staining by the periodic acid-Schiff method, found a hyalinization in the terminal arterioles leading to a gradual occlusion of their lumina. Examination of fundus photographs of eyes showing P.D.R. has revealed evidence of arteriolar involvement in 19 out of 112 eyes (17.9 percent). This arteriolar involvement shows as a bright white line replacing the blood column of the vessel involved (fig. 2). The vessels are commonly of the third or fourth arteriolar branching or smaller. The "white line" usually commences at the bifurcation of an arteriole, one branch of which remaining unchanged and the other being converted to a "white line" which can often be traced several disc diameters to its termination. Although this hyalinization must be considered a pathological condition, it does not necessarily follow that there is complete obliteration of its blood column. That some contain blood, albeit an attenuated column, is evidenced by direct observation. Firstly, if the white line is traced peripherally, here and there, it is missing and a view of the blood column can be obtained. Secondly, when using the light coagulator in the vicinity of these vessels, the brilliant illumination during an actual coagulation, which is much more intense than the ophthalmoscope, reveals a fine blood column in the middle of some of the white

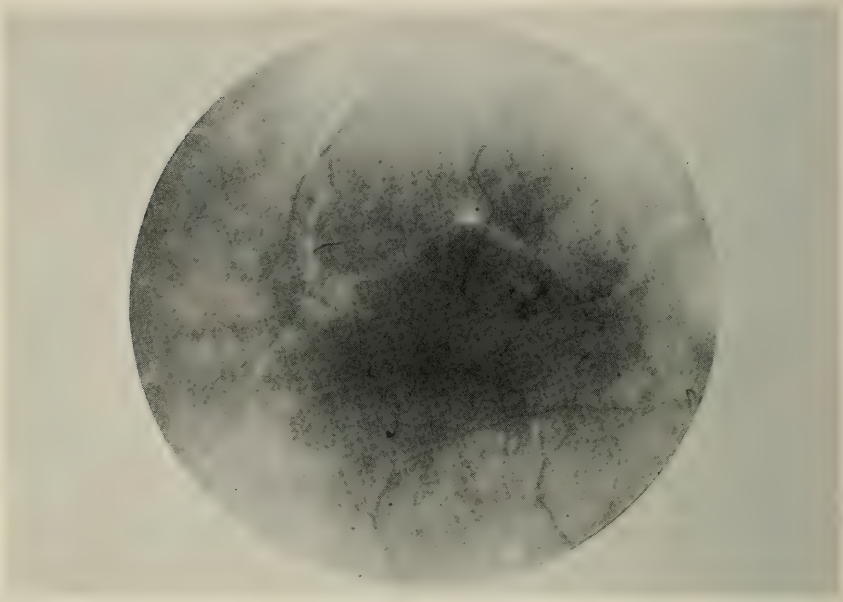

FIGURE I.—*Macula area. Late changes in proliferative diabetic retinopathy. Note the macular pigmentation and irregular connective tissue formations in the choroid.*

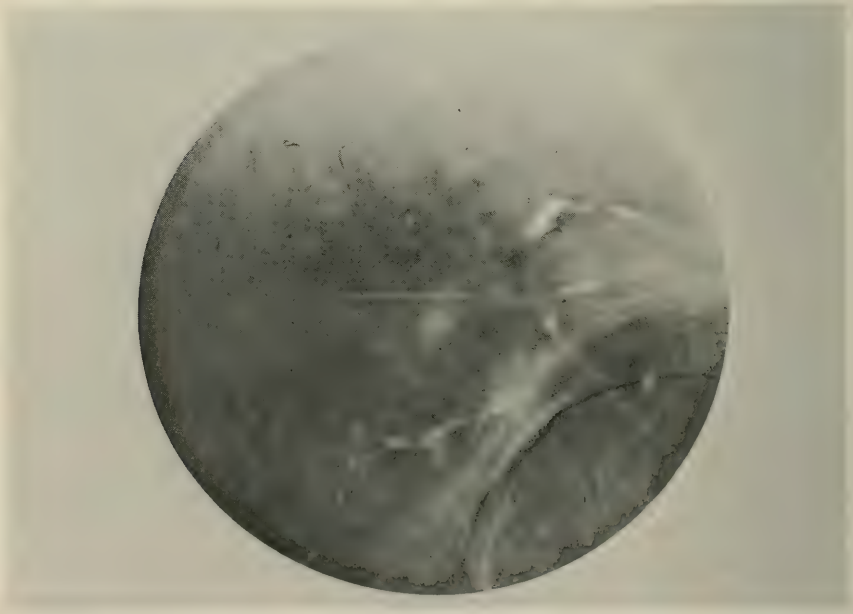

FIGURE II.—*Equatorial area. A typical hyalinization of smaller arterioles giving a "white line" appearance.*

lines. Furthermore in the arterial phase of a fluorescein injection an apparently fibrosed vessel may be shown to have a normal blood column.

The same "white line" appearance is not infrequently found in arteriosclerotic subjects with or without hypertension. Although the white lines in P.D.R. may be found in relatively early stages and are not necessarily related to the formation of new vessels, they are an interesting concomitant.

Further observations of the arterial side of the circulation and its relation to generalized vascular disease are being carried out.

Rubeosis of the iris and secondary glaucoma

This complication occurred in 10 eyes (8.9 percent). In three cases it was bilateral.

Retention of Vision after 5 Years (Table II)

Seventeen patients have been followed for over 5 years, and all eyes but one had stage I lesions at the time of the original observation. Three patients have died blind. Thirty-three eyes are available for study; one eye is excluded because it has been successfully light coagulated. Four other light-coagulated eyes are included because this was done unsuccessfully on unsuitable cases and did not influence the progress of the disease.

Of the five eyes in which vision was unchanged, two eyes, from the same patient had a complete regression of multiple stage I lesions. The case was reported in the original 1964 series and 5 years later the new vessels have not reappeared. In another case there has been an exceptionally slow development of stages I and II in both eyes and in the fifth eye of this group stage I extended 4 years.

The three eyes which have retained vision (6/9, 6/12 and 6/36) albeit reduced vision, show marked stage III lesions.

Conclusions from 8 Year Survey

Once the new vessels of P.D.R. have appeared they evolve in a predictable manner through a hypertrophic stage into an atrophic stage. When in the hypertrophic stage the eye is liable to disastrous hemorrhages and effects secondary to these hemorrhages. In passing into the atrophic stage, other secondary lesions are caused by cicatricial

TABLE II.—*Retention of vision after 5 years (33 eyes, 17 patients)*

	Eyes	Patients
(1) Sighted:		
(*a*) With visual acuity unchanged	5	3
(*b*) With reduced vision	3	3
(2) Blind	25	11
Total	33	17

changes in the vitreous, retina and choroid. It is abundantly clear that the primary aim of treatment must be the inhibition or eradication of the primary lesions while they are in an early stage of development. If this is achieved an increasing number of eyes will be preserved to join the small group which, in the natural evolution of the disease, settle into a quiescent state in which reasonable vision is preserved for a considerable number of years.

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CHAPTER 6

The Natural History of Diabetic Retinopathy

EVA M. KOHNER, B.Sc., M.B., M.R.C.P.
COLIN T. DOLLERY, M.B., M.R.C.P., F.R.C.P.

Previous studies of the natural history of diabetic retinopathy have relied upon visual or photographic comparisons of lesions or on grading the severity of different features seen on retinal photographs (*1*). These methods are relatively insensitive and only semiquantitative. In this paper we give a preliminary assessment of new quantitative methods applied to the study of retinal microvascular disease, particularly microaneurysms and cotton-wool spots.

PATIENTS AND METHODS

1. *Patients studied*—Eighteen patients with established retinopathy were selected for study because they were willing to attend for repeated examination and it was technically feasible to obtain high quality retinal photographs. Seven patients with severe retinopathy were drawn from the control group of a clinical trial of pituitary ablation (one had refused ablation). The other 11 were found to have retinopathy during a diabetic clinic survey.

All the patients had both color and fluorescence photographs taken at intervals varying from 6 weeks to 6 months over a period of approximately 2 years. Fifteen patients had intravenous fluorescence angiograms, while 3 had both intra-arterial and intravenous studies (*2*, *3*). A color survey of the fundus was taken on each occasion, while fluorescein angiograms were taken of the areas with the most marked abnormalities or those with especially interesting features.

2. *Analysis of photographic material*—Color and fluorescence pictures of the same areas were projected side by side for accurate comparison. Areas of capillary closure and of cotton-wool spots were drawn from the projected pictures and their area measured using a planimeter. The position of microaneurysms present on the initial study in any given area was plotted on a map drawn on transparent copy paper from prints of that area. On subsequent studies different symbols were used to indicate whether the microaneurysms were still present, had disappeared or were a new feature. From this map it was

The Department of Medicine, Royal Postgraduate Medical School, Ducane Road, London, W. 12. England.

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possible to calculate the rate of disappearance of microaneurysms, as a proportion of those present initially, and the rate of formation of new aneurysms as the number of microaneurysms per square millimeter of retina in a given time in a particular area. The number of microaneurysms surviving from the first study at different times was plotted on semilogarithmic paper against time to estimate the half-life or disappearance rate of a given set of aneurysms.

RESULTS

The life history of microaneurysms—In seven areas in five patients there was a reduction in the number of microaneurysms initially present to 50 percent within 7 months. In the other 13 patients studied, over 50 percent of the aneurysms present initially remained at the end of a period from 8 months to 2 years.

If the disappearance rate of microaneurysms was uniform, the semilog plot of the number surviving against time should give a straight line. This was not the case in these studies. The plot was alinear and the line fell more rapidly in the early months than later. At present we have insufficient data to decide whether or not there are two or more distinct populations of aneurysms but this seems unlikely. Probably there is a wide range of microaneurysms' half-lives.

In some areas where color pictures indicated an apparent improvement in retinopathy (figs. 1 and 2) fluorescence studies showed that when microaneurysms disappear, capillary closure may develop (figs. 3, 4, 5, and 6) with arteriolar occlusion. A similar sequence of events was seen in five areas of four patients.

Formation of aneurysms—The total number of microaneurysms in any one area was variable and must depend upon their rate of disappearance and formation. New microaneurysms tended to form all of the time in all 18 patients. The rate of formation was different in different parts of the retina and at different times. The range was from 0.1/mm.^{2}/month to 3.5/mm.^{2}/month. However, with few exceptions, if there was an increase in the formation rate in one area there was also an increase in others (except when microaneurysms were replaced by areas of capillary closure). This suggests that it is general rather than local factors which influence the rate of formation of microaneurysms. The wide variation between individual rates of formation and disappearance of microaneurysms makes statistical comparisons difficult at the present time. No definite correlation existed between the disappearance and formation rate of microaneurysms. In only six patients was there a significant correlation between the total number present and the rate of new aneurysm formation.

FIGURE 1.—*From a color picture of the right superior temporal region. The first arrow (A_1) shows an area of microaneurysms (MA) and the second arrow (A_2) a cotton-wool spot.*

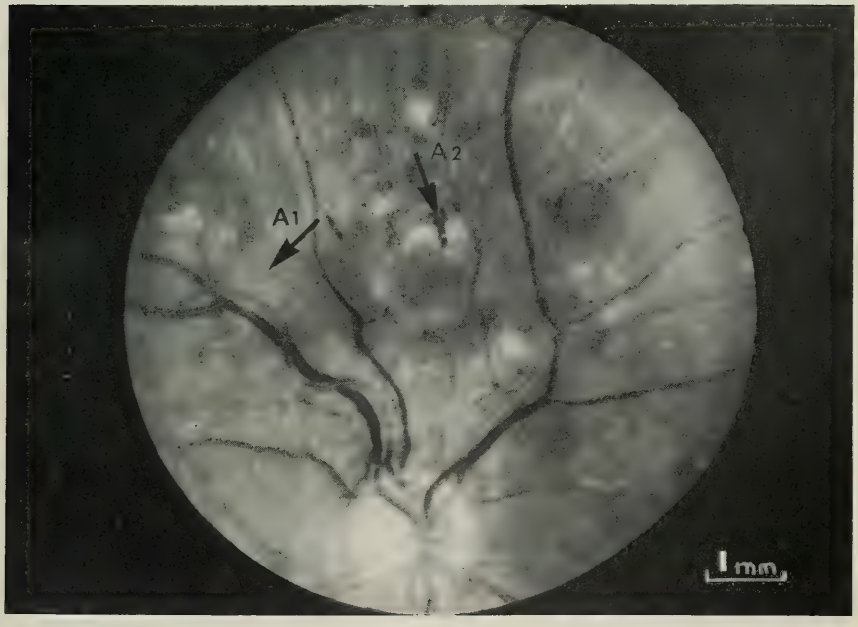

FIGURE 2.—*Same area as figure 1 but 6 months later. The microaneurysms (A_1) have cleared but the cotton-wool spot remains (A_2).*

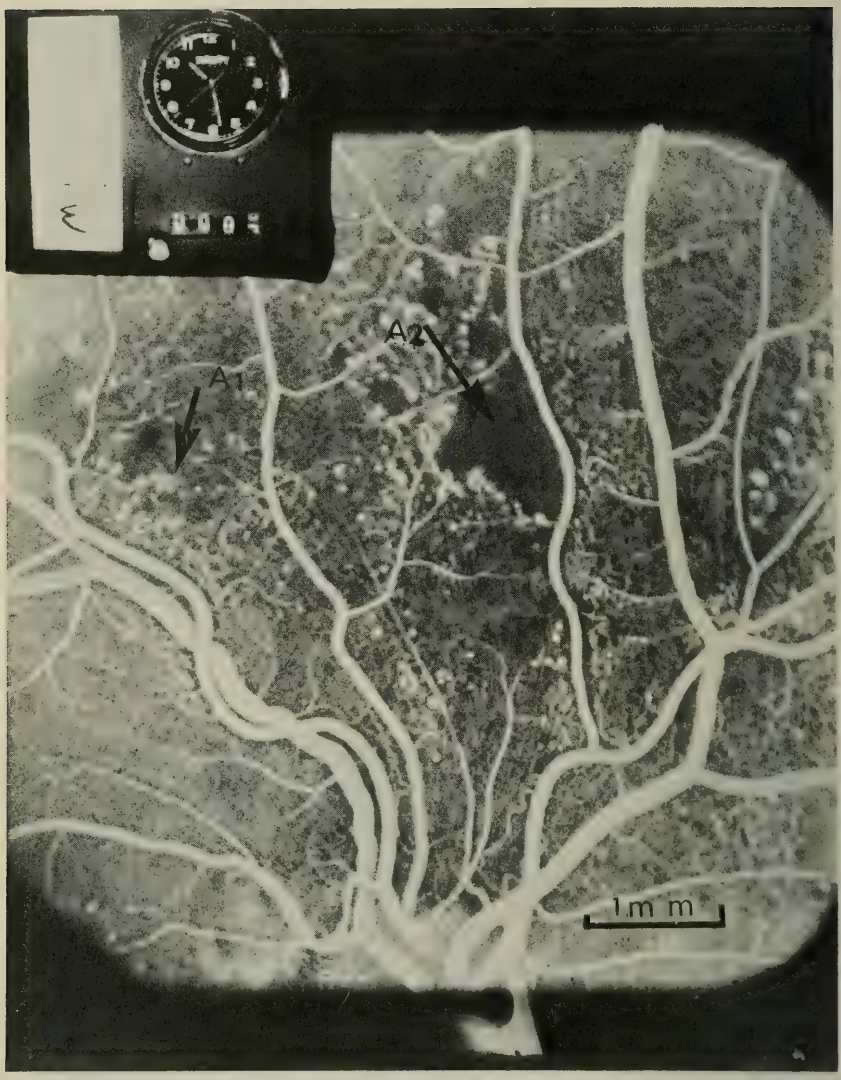

FIGURE 3.—*Fluorescence angiogram of the same area as figure 1. The first arrow (A_1) shows an abnormal arteriole surrounded by microaneurysms; and the second (A_2) the region of the cotton-wool spot with capillary closure and a ring of microaneurysms.*

Some microaneurysms were not perfused on every occasion they were studied. Apparent closure of a microaneurysm, followed by a reopening was observed in 10 of the 18 patients studied. Blood flow through microaneurysms may be variable due to hemodynamic factors, and it is conceivable that the original microaneurysm occluded and a new one formed very close to it. Some apparent differences may also be

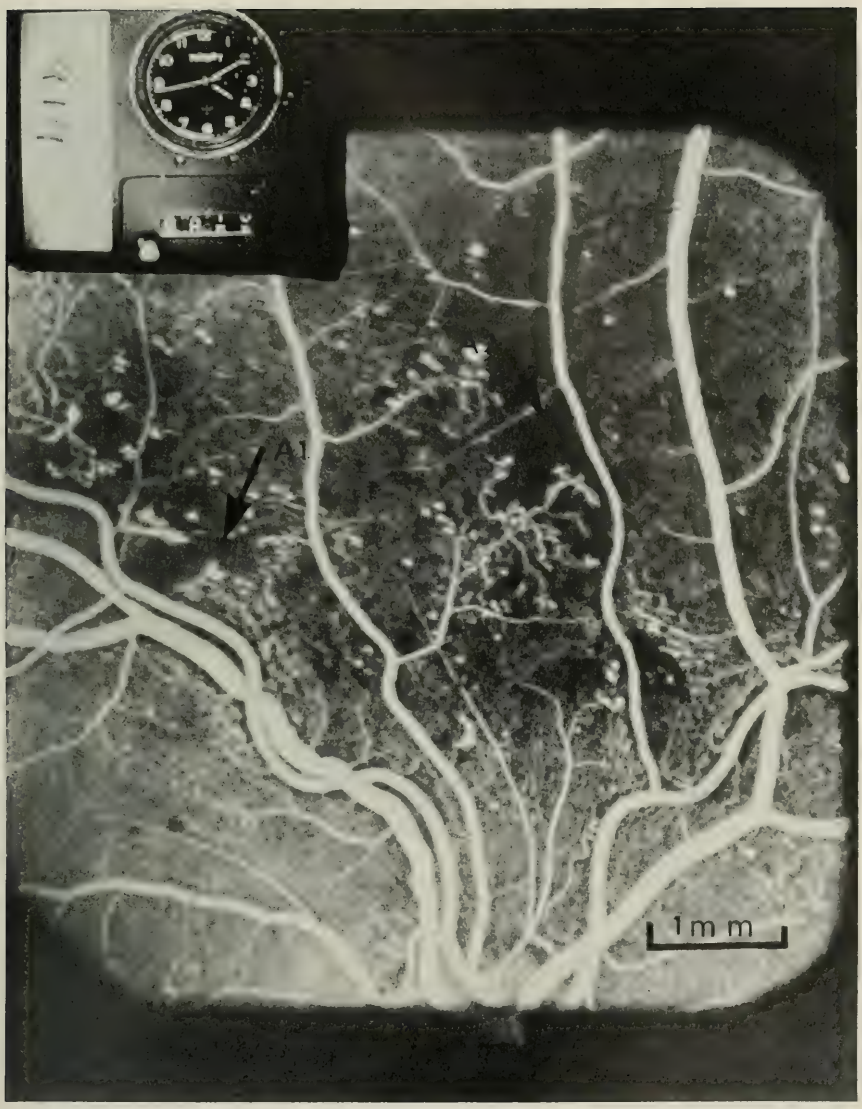

FIGURE 4.—*The same area as figure 2. The capillary bed surrounding the abnormal arteriole is no longer perfused (A_1) while new vessels are growing into the area of the cotton-wool spot.*

accounted for by differences in the quality of the angiograms but this is unlikely to explain all of the examples observed.

Capillary closure and cotton-wool spots—Areas of capillary closure or nonperfusion were observed in all but two of the 18 patients. These areas varied from about 0.1 millimeter to several millimeters in diameter. Some of the larger areas of capillary closure were associated

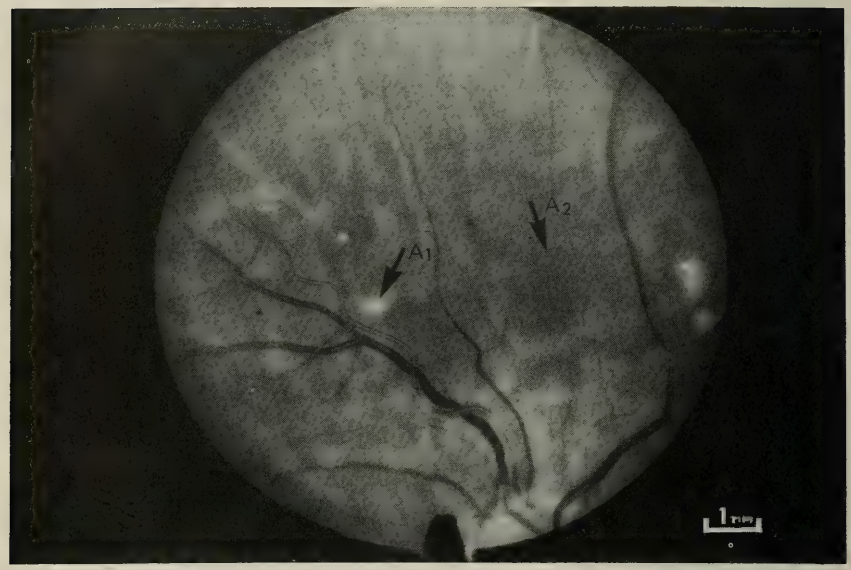

FIGURE 5.—*Same as Figure 1 but 2 years later. A cotton-wool spot has formed in the area supplied by the abnormal arteriole (A_1) while the other cotton-wool spot has cleared (A_2).*

with cotton-wool spots on color photographs. There was no relation between the patient's blood pressure and the presence of cotton-wool spots, as already noted by Esmann et al. (*4*). As in hypertensive patients, cotton-wool spots in diabetics were usually preceded by a greyish-white area in the retina, and abnormal arterioles could be seen at times even on color photographs (fig. 7). The survival time of the cotton-wool spots was very much longer than that observed by Hodge and Dollery (*5*) in hypertensive patients. This long survival was especially marked in patients over the age of 40 (fig. 8). In only one of nine patients in this age group did a cotton-wool patch disappear within 12 months, while it did so in three out of six patients during this time interval in the younger age group (fig. 9).

On fluorescence angiograms, the cotton-wool patches were surrounded by abnormal capillaries and a ring of microaneurysms (figs. 3 and 6). The number and size of the microaneurysms tended to decrease gradually over a period of time, even when capillary closure persisted. Marked abnormalities of the arterioles were frequently observed adjacent to cotton-wool spots and not only was the arteriole supplying the area occluded but the parent arteriole was also abnormal (fig. 10). The abnormalities included narrowing, irregular outline with localized dilation, and sometimes leakage into the arterial wall. Even when cotton-wool patches disappeared, the area of capillary closure usually

FIGURE 6.—*Fluorescence angiogram of figure 5. The area of capillary closure in which the cotton-wool spot has formed has increased in size (cf. figure 4) and the arteriole is occluded. Further ingrowth of vessels in the second area (A_2).*

persisted (figs. 11 and 12) and in only one area was an arteriole observed to reopen. It is interesting to note that arteriovenous communications developed in four areas of capillary closure during the period of observations. These were true shunt vessels, being of larger diameter than capillaries (fig. 13).

Some degree of revascularization of areas of capillary closure was observed in four areas in three patients. The ingrowth of capillaries

from the venous side of the surrounding capillary bed was, however, very slow (figs. 3, 4, and 5).

DISCUSSION

The natural history of diabetic retinopathy is variable. Many observers have noted that not only progression but also spontaneous regression of lesions. (*6*, *7*, *8*, *9*). Earlier studies have used nonquantitative methods. In this paper we present a preliminary appraisal of new methods which yield quantitative results in the study of microaneurysms, capillary closure and cotton-wool spots.

Microaneurysm counts over a small area are accurate and reproducible and give the best promise of a quantitative approach to the turnover rate of capillary lesions. Both the rate of formation and of disappearance of microaneurysms proved to be extremely variable.

FIGURE 7.—*From a color photograph of a young normotensive diabetic patient. There is a cotton-wool spot (A_1) and the main arteriole supplying this segment of retina is narrowed at its origin (A_2).*

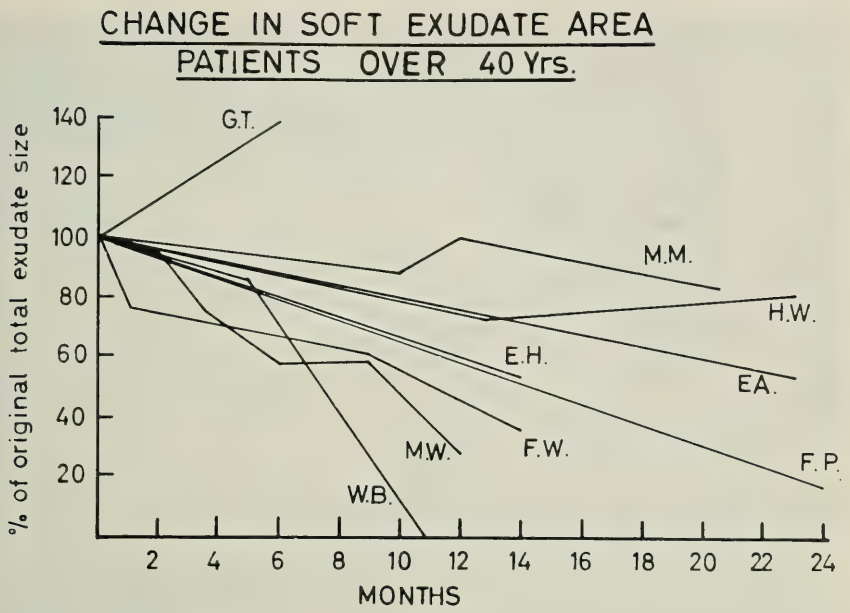

FIGURE 8.—*Change in total area of cotton-wool spots plotted against time in patients over 40.*

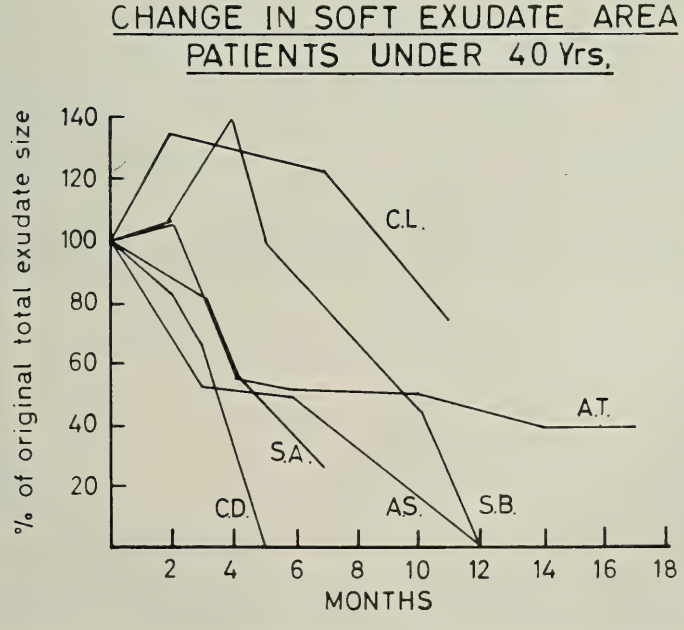

FIGURE 9.—*Change in total area of cotton-wool spots plotted against time in patients under 40.*

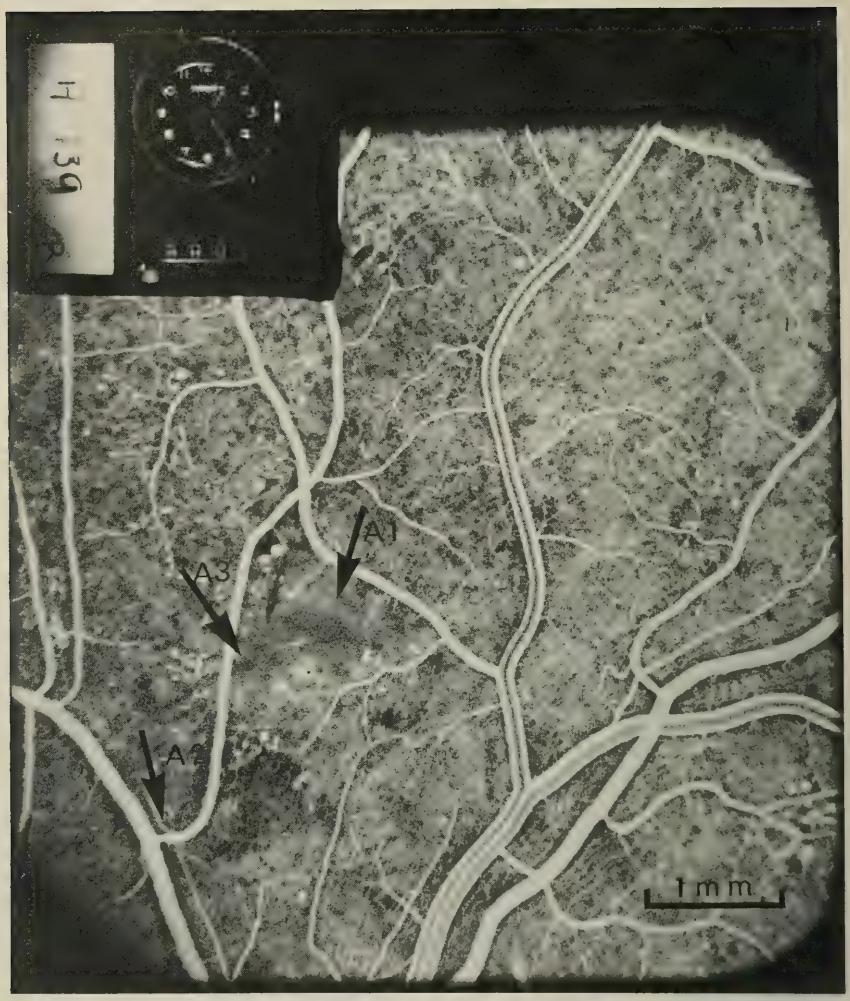

FIGURE 10.—*Fluorescence angiogram of same area as figure 7. The arteriole (A_3) feeding the area of cotton-wool spot (A_1) is occluded.*

If the microaneurysms were a uniform population their disappearance rate should be uniform on a semi-log plot. This was not the case. There may be many reasons for this variability. More than one process may be involved in the obliteration of aneurysms and factors such as the initial size and vascular connections may play a part. Further study will be needed to evaluate these different factors.

The total number of microaneurysms represents a balance between the rate of formation and disappearance. The factors affecting the rate of formation and disappearance may be quite different. For example,

the rate of formation might be a measure of the activity of the disease process damaging the small vessels while the rate of disappearance may depend upon reparative processes which either thrombose the aneurysms or remodel the capillary wall. We cannot throw any light on these very interesting questions at present.

Capillary closure was only occasionally associated with cotton-wool spot formation. Only when the main arteriole itself was occluded did a cotton-wool spot appear. It is probable that both the presence of a major arteriolar occlusion as well as the rate at which occlusion develops is important in the formation of a cotton-wool spot. This could account for the absence of cotton-wool spots in some areas where large arterioles were occluded. Some of these areas may have been the site of a cotton-wool spot that had already disappeared, but this is unlikely in view of the long survival of cotton-wool spots noted.

The slow disappearance of the cotton-wool spots in these diabetic patients compared with hypertensives could be due to the abnormality

FIGURE 11.—*Same as figure 9 but 15 months later. Cotton-wool spot (A_1) has cleared but the origin of the arteriole (A_2) is still narrow.*

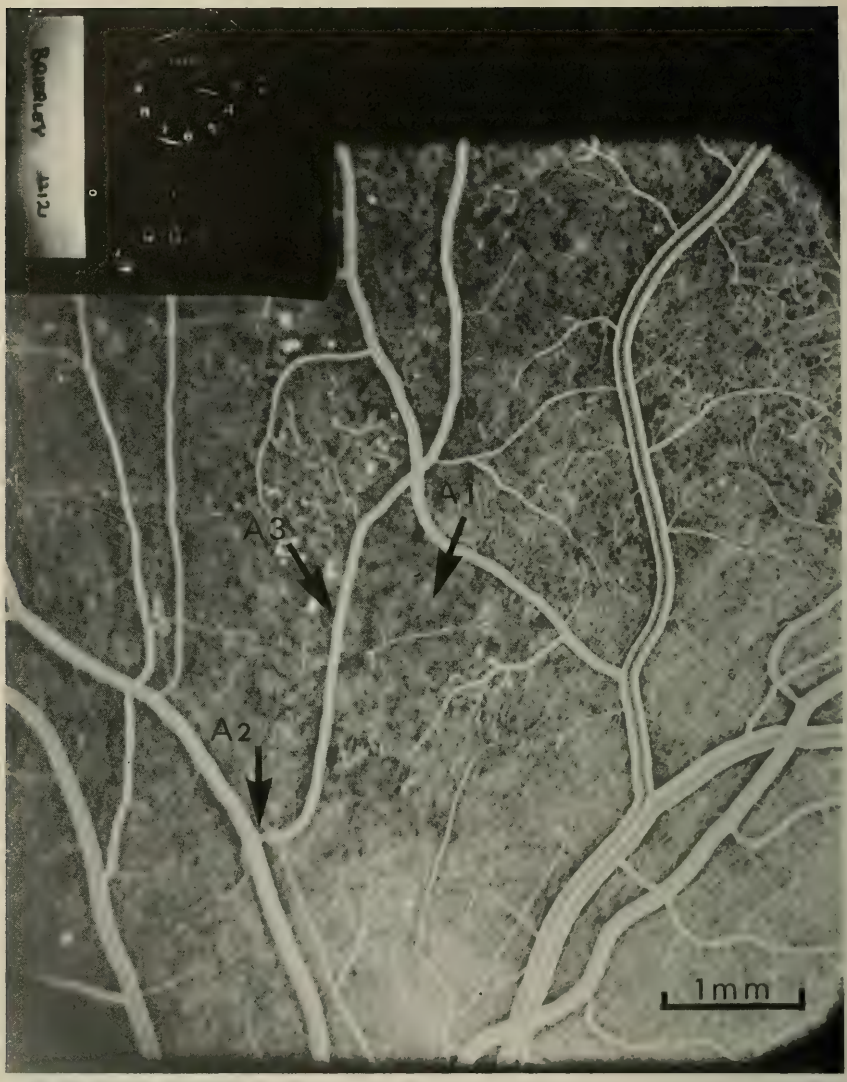

FIGURE 12.—*Fluorescence picture of same area as figure 11. The cotton-wool spot disappeared but capillary closure persists (A_1). Note also retrograde filling of arteriole.*

of the surrounding capillary bed, delaying the clearance of cellular debris by macrophages. Alternatively, the macrophage function itself may be abnormal in diabetes.

In hypertensive patients when cotton-wool spots disappear the capillaries are perfused again. In diabetics this is not the case. Since

FIGURE 13.—*Same as figure 12, but 3 months later. Capilary closure is still present* (A_1) *but the arteriole* (A_3) *has reopened and an AV shunt has formed* (A_4).

here the arteriolar involvement is secondary to widespread capillary disease, as observed by Ashton (*10*), reopening of the arterioles alone would be of little help. Capillaries do not become reperfused but have to reform and this is a very much slower process.

SUMMARY AND CONCLUSIONS

1. Serial color and fluorescence photographs were taken in a group of 18 diabetic patients to study the evolution of the capillary abnormalities.

2. An attempt has been made to quantitate the rate of disappearance and formation of microaneurysms. The rate of disappearance of microaneurysms was variable in different patients and in different areas of the same patients. The rate of formation of new aneurysms was variable, but an increased rate of formation in one area was usually associated with an increased rate of formation in other areas of the same retina. While an increase in the rate of formation usually indicates worsening of the retinopathy, disappearance of aneurysms does not necessarily mean improvement, as it may be followed by capillary and arteriolar occlusion.

3. Areas of capillary closure were common, and some were associated with cotton-wool spots. Cotton-wool spots persisted for many months, some for over 2 years. Even when they disappeared, the area of capillary closure persisted. In only two patients was revascularization of the area of capillary closure seen, while shunt vessels developed in four.

Acknowledgments

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We also thank Miss R. Crowe who developed the films and made the illustrations.

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CHAPTER 7

The Natural Course of Diabetic Retinopathy: A Clinical Study of 321 Eyes Followed One Year or More

FRANK L. MYERS, M.D.
MATTHEW D. DAVIS, M.D.
YVONNE L. MAGLI, B.S.

The purpose of this paper is to present a group of untreated cases of diabetic retinopathy to which the O'Hare classification has been applied, and against which the results of various modes of therapy to be presented at this conference can be compared.

The records of all patients seen in the Diabetic Retinopathy Clinic at the University of Wisconsin during the years 1961 through 1966 were reviewed. Written descriptions, fundus diagrams and fundus photographs were utilized for classification of each eye at the initial and final visits. Corrected visual acuities at the initial and final visits were recorded as well as visual acuities at the first visit following the elapse of 1, 3, and 5 years from the initial visit (table I). The majority of the patients in this group were referred because of visual impairment, and the group as a whole is therefore not representative of an unselected diabetic population. Patients with both juvenile and adult onset diabetes were included in approximately equal numbers. Although many patients were receiving various medications such as vitamins C and K, rutin, bioflavinoids, etc., both prior to and during the course of this study, no effect on the course of the retinopathy was recognized and they therefore have been ignored. Twenty-six patients underwent pituitary ablative procedures and in 20 eyes photocoagulation was carried out. These eyes were considered only during the period from initial observation until treatment and were excluded thereafter. Two eyes which underwent scleral buckling operations for retinal detachment were included in the study.

Three hundred and twenty patients were examined during the period covered by this report, yielding 629 eyes for analysis. Of this number,

From the Department of Surgery (Ophthalmology), University of Wisconsin, Medical School, Madison, Wis.

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40 eyes had no evidence of diabetic retinopathy initially. Five of these eyes developed background retinopathy during the period of observation but none of the 40 were included in this series. Of the remaining 589 eyes with diabetic retinopathy, 268 were followed for periods less than 1 year and were therefore excluded. Thus, a total of 321 eyes remained for the following analysis. These eyes were examined at intervals over a period of 1 to 7 years (mean 2.7 years).

Table I summarizes our results. Column one lists all the categories of the O'Hare classification [1], with the number of eyes belonging to each category at the initial visit recorded in column two. The number of eyes which at the final visit were still in the same category or a less severe one is shown in the third column. An increase in any one of the components N, F, or H was sufficient to remove the eye concerned from the "same or better" group. The number of eyes with visual acuity at the final visit that was the same as or better than visual acuity at the initial visit is recorded in the fourth column.

It is readily apparent that in only a few categories were there sufficient eyes for valid comparison with other categories. In general the number of eyes retaining initial (or better) vision at the final visit was less than the number remaining in their initial (or better) categories of the classification. This tendency reflects the fact that marked progression is usually required to move an eye into a more severe category in the O'Hare classification. Furthermore, in the case of eyes in the more severe categories, the classification provides very limited means to indicate further progression. The classification was designed chiefly to allow separation of eyes into a few large groups so that results at different centers could be compared, rather than for following individual eyes, and it is apparent that it is not suitable for the latter purpose. Since the ultimate aim of treatment is to maintain visual function, particularly central acuity, use of visual acuity as the major criterion for judging results seems quite satisfactory, particularly over long periods.

In attempting to compare our visual results with those of other workers, the problem of length of followup became apparent. Since diabetic retinopathy is usually progressive, the longer the followup the fewer will be the patients maintaining their initial classification and vision. Calculation of a mean followup period for a group of patients is not very helpful, and only fortuitously would comparable figures arise from studies at different institutions. It therefore seems desirable to adopt generally agreed upon followup periods and to report results in each patient at the end of such periods rather than at their most recent visit. Our data has been treated in this manner

[1] O'Hare classification, p. XXI.

in regard to visual acuity and the results recorded in columns five through seven of table I. Disparities between the 1-year data and the last-visit data are the result of improvement of vision at the time of their final visit in some eyes.

It is of interest that one-third of our cases of nonproliferative (category B) retinopathy progressed to the proliferative stage during the relatively brief period of observation. This would seem to be at variance with the study of Burditt et al. (*1*). However, the majority of our patients were referred because of visual symptoms and many of the eyes with nonproliferative retinopathy were fellow eyes of those with proliferative retinopathy. It is therefore not surprising to find more rapidly progressive retinopathy in our patients than in a survey of a general diabetic clinic population.

No eyes have been excluded because of poor initial visual acuity, and it is of interest to know how much the results may have been influenced by eyes with initially very poor vision (hand movements or less) which are counted as maintaining same or better visual acuity at their final visit, i.e., as "successes." There were 18 eyes with initial visual acuity of hand movements or less and of these eight maintained their initial or better acuity.

The choice of maintenance of initial or better visual acuity at the final visit as a criterion for "success" is certainly open to criticism, and in table II we have therefore summarized our data on 171 eyes with initial visual acuity of 20/40 or better using as the criterion of "success" maintenance of 20/40 or better acuity. Thus an eye with initial vision of 20/15 which falls to 20/40 is still considered a success, but any eye with final vision of less than 20/40 is recorded as a "failure." When considered in this way these eyes, as might be expected, did better visually than the larger group in table I.

In table III are listed the immediate causes of visual loss in 200 eyes that had vision reduced to 20/40 or worse for periods of 6 months or more. It is significant that macular edema, occurring in most instances in eyes with nonproliferative retinopathy, is the third most common cause of visual loss in this series.

SUMMARY

Three hundred and twenty-one eyes with diabetic retinopathy were followed for 1 year or more and assigned an initial classification using the O'Hare system. These were analyzed with reference to (1) the status of their vision at 1 year, at the final visit, and at 3 and 5 years when available; (2) the status of their classification with regard to

TABLE I.—*Summary of 321 eyes with diabetic retinopathy followed 1 year or more*

Initial visit		Last visit		Eyes vision same or better after number followed		
Classification	Number eyes	Classification same or better than initial	Vision same or better than initial	1 year	3 years	5 years
B	115	75(65%)	46(40%)	61/115(53%)	14/38(37%)	4/8
BH_1	5	1	1	3/5	0/1	
$N_1F_0H_0$	47	16(34%)	17(35%)	23/47(49%)	8/14	4/6
$N_2F_0H_0$	24	8(33%)	6(25%)	8/24(33%)	2/7	
$N_1F_1H_0$	6	3	3	2/6	1/1	0/1
$N_2F_1H_0$	3	2	3	1/3		
$N_1F_2H_0$	4	3	0	0/4	0/1	
$N_2F_2H_0$	6	2	1	2/6	1/3	0/1
$N_1F_0H_1$	15	3(20%)	3(20%)	5/15(33%)	2/6	1/4
$N_2F_0H_1$	5	1	1	1/5	1/3	0/1
$N_1F_1H_1$	17	5(29%)	4(23%)	6/17(35%)	4/7	2/5
$N_2F_1H_1$	9	2	3	4/9	0/4	
$N_1F_2H_1$	15	12(80%)	7(46%)	9/15(60%)	7/7	2/4
$N_2F_2H_1$	20	17(85%)	4(20%)	8/20(40%)	0/4	0/2
$N_0F_1H_0$	1	1	0	1/1		
$N_0F_2H_0$	2	0	1	0/2	1/2	1/2
$N_0F_1H_1$	2	1	1	1/2	1/1	
$N_0F_2H_1$	6	5	3	5/6		
H_2	19	[1]19	12(63%)	12/19(63%)	2/2	2/2
Totals	321	176(55%)	116(36%)	152/321(47%)	44/101(44%)	16/36(44%)

[1]Includes 10 eyes which improved and 9 which remained the same.

TABLE II.—*Summary of 171 eyes with vision 20/40 or better at initial visit followed 1 year or more*

Initial visit		Last visit		Eyes with vision 20/40 or better after number years followed		
Classification	Number eyes 20/40 or better	Classification same or better than initial	Vision 20/40 or better	1 year	3 years	5 years
B	86	56(65%)	62(72%)	70/86	17/30	4/7
$N_1F_0H_0$	32	11(34%)	22(69%)	25/32	7/10	4/4
$N_2F_0H_0$	17	6(35%)	9(53%)	11/17	3/5	
$N_{1,2}F_{1,2}H_0$	9	5	7	7/9	1/2	1/2
$N_{1,2}F_0H_1$	9	3	4	2/9	2/4	1/2
$N_1F_1H_1$	7	2	0	1/7	1/4	0/3
$N_2F_1H_1$	2	1	1	2/2	1/1	
$N_1F_2H_1$	4	2	1	1/4	2/2	1/2
$N_2F_2H_1$	5	5	3	3/5	1/1	
Total	171	91(53%)	109(64%)	119/171	35/59	11/20

TABLE III.—*Causes of visual loss in 200 eyes with visual acuity of 20/40 or less over periods of 6 months or more*

Cause of visual loss	Number of eyes	Number improved
Severe vitreous hemorrhage	66	14
Macular detachment	47	1
Macular edema	35	3
Hemorrhagic glaucoma	26	None
Tension lines in macula	13	None
Macular exudate	9	None
Macular pigment	9	None
Cataract	9	2
Generalized retinal ischemia[1]	3	None
Macular hemorrhage	0	----------

[1] Marked sclerosis of the retinal vessels without other demonstrable cause of visual loss.

progression during their total length of followup; and (3) the cause of visual loss if this occurred.

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CHAPTER 8

Visual Prognosis in Advanced Diabetic Retinopathy

ARNALL PATZ, M.D.
JOSEPH W. BERKOW, M.D.

An observation by the staff of the Seeing Eye, Inc., that blind diabetic individuals rarely returned to the Seeing Eye for a second guide dog prompted our interest in the study of the visual prognosis in diabetic patients. The Seeing Eye is an institution dedicated to the training of guide dogs for blind people and since the institution was founded several thousand people have been trained in the use of the guide dogs. Approximately 200 of these were diabetics. The diabetics, however, in contrast to other blind patients, rarely returned to the Seeing Eye for a second dog. In order to study these people, we were kindly permitted to examine the records of the approximately 200 blind diabetics who had received guide dogs as of November 1964. Of this group of people there was sufficient information on 180 to carry out a retrospective study. The group consisted of 85 deceased and 95 living diabetics. Approximately two-thirds were male and one-third female in this group.

An analysis of our data from this study has been previously reported (*1*). A summary of the results is as follows: In most of the patients, who were under 20 at the time their diabetes was discovered, the interval from the discovery of diabetes to the onset of severe blindness [1] was an average of 17.4 years (fig. 1). The duration of blindness prior to death in the group of 85 deceased diabetics was an average of 5.8 years (fig. 2). Since the useful life of the guide dog is from 7 to 10 years, it was apparent why the blind diabetics rarely requested a second guide dog from the Seeing Eye.

The short mean survival of 5.8 years following blindness for these young diabetics was especially significant since all candidates had to be in reasonably sound health to qualify for a guide dog; e.g. to have the stamina to walk briskly with a large dog several miles each day.

[1] Severe blindness was designated as the level of vision recorded on the application for a guide dog. This was a much lower level of visual acuity than legal blindness. In over one-half of the patients vision was reduced to light perception or poorer; the best documented vision was for one patient with 10/200 in one eye and 3/200 in the other.

From the Filbert Foundation Laboratory, Wilmer Ophthalmological Institute, Johns Hopkins Hospital and University, Baltimore, Md.

These studies were aided by grant no. NB–0446, National Institute of Neurological Diseases and Blindness, Public Health Service.

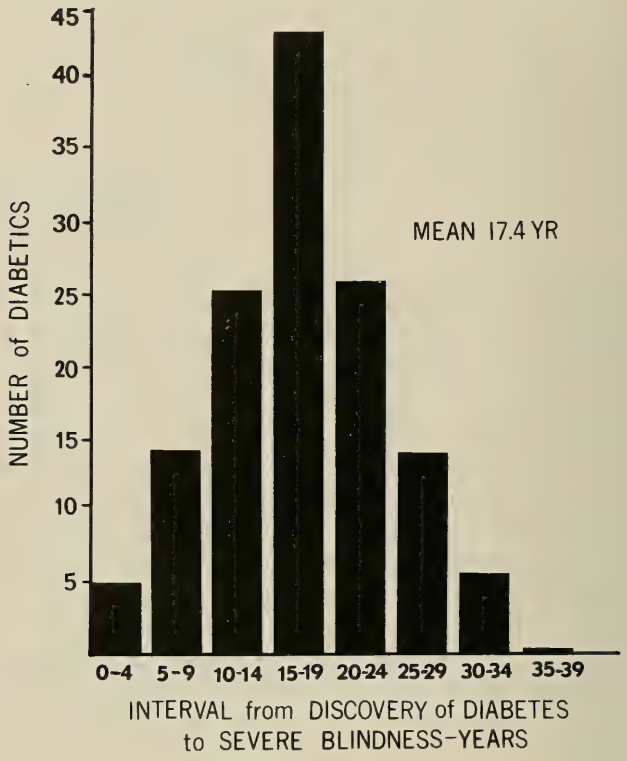

FIGURE 1.—*Interval from discovery of diabetes to onset of blindness in 135 diabetics from the Seeing Eye, Inc.*

It should be pointed out that the mean of 5.8 years was the period from "severe blindness" to death and not from the onset of proliferative diabetic retinopathy to death.

Recently we studied the natural course of visual deterioration in a selected group of patients with severe proliferative diabetic retinopathy (*2*) (N_1 and N_2; F_1 and F_2—O'Hare classification).[1] Patients who developed cataracts sufficient to cause grossly impaired vision, and patients who had either hypophysectomy or photocoagulation therapy were excluded from the study. Each of the diabetic patients had impaired vision (visual acuity 20/200 or poorer) in one eye, but had retained 20/80 or better vision in the second eye. The documented date that the first eye had deteriorated to 20/200 or poorer was recorded and the duration of "useful" vision (20/80 or better) of the second eye was then studied.

[1] O'Hare Classification, p. XXI.

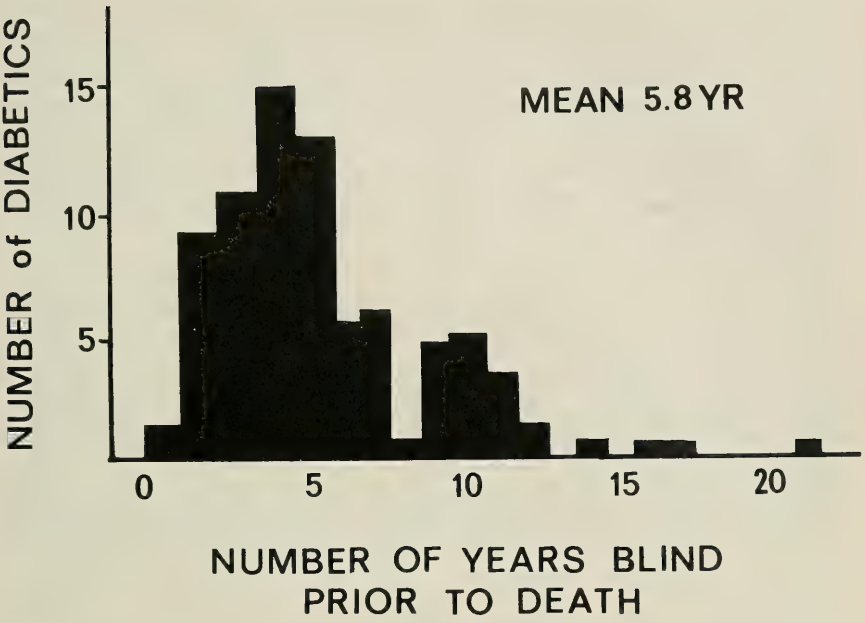

FIGURE 2.—*Duration from onset of blindness to death in 85 diabetics from the Seeing Eye, Inc.*

These diabetic patients who had lost useful vision in one eye but retained it in the second eye might have been considered on the basis of their ocular status as candidates for hypophysectomy. The fate of their vision in the second eye illustrates the natural course of the disease in this untreated group and may serve as a reference for comparison with hypophysectomy studies.

Figure 3 shows the course of 27 patients followed over a 5-year period. In 16 patients (59 percent), the visual acuity of the second eye decreased during the first 12 months to 20/200 or worse and remained so for the duration of the study. Eight patients (30 percent) lost vision in the second eye during the following 4 years of followup; three patients (11 percent) maintained in the second, or better eye, useful vision (20/20 to 20/80 visual acuity) at the end of the 5 years. One patient showed an exception to the usual course. This 59-year-old male diabetic of 20 years' duration demonstrated a reversal of the better and poorer eye. On entering this study the right eye showed hand motion vision due to a large vitreous hemorrhage (H_2). Later the hemorrhage cleared and the vision in the right eye improved to, and was sustained at, the 20/50 level. The originally better left eye decreased to 10/200 vision after 3 years and remained severely impaired at this level.

The small number of cases in this study permits only limited conclusions on visual prognosis in severe proliferative retinopathy. The rate of visual deterioration was found to be consistent with that which might have been predicted from the series of Beetham (*3*) and of Deckert and coworkers (*4*). Beetham (*3*) found an average rate of change per eye of 1.9 years to progress in his classification from "slight" to "moderate" and 1.6 years for a change from "moderate" to "marked" proliferative retinopathy.

Deckert and coworkers (*4*) correlated the rate of visual deterioration with the severity of the diabetic retinopathy. They found the visual prognosis of the individual eyes depended on the extent and localization of proliferative changes. Half of the eyes with localized peripheral proliferative changes became blind in 5 to 6 years, while in eyes with prepapillary or peripapillary proliferations, half became blind within 2 to 3 years.

Further analyzing the 24 cases of our series (fig. 3) who lost vision in their second eye, we see that 16 (66⅔ percent) occurred during the

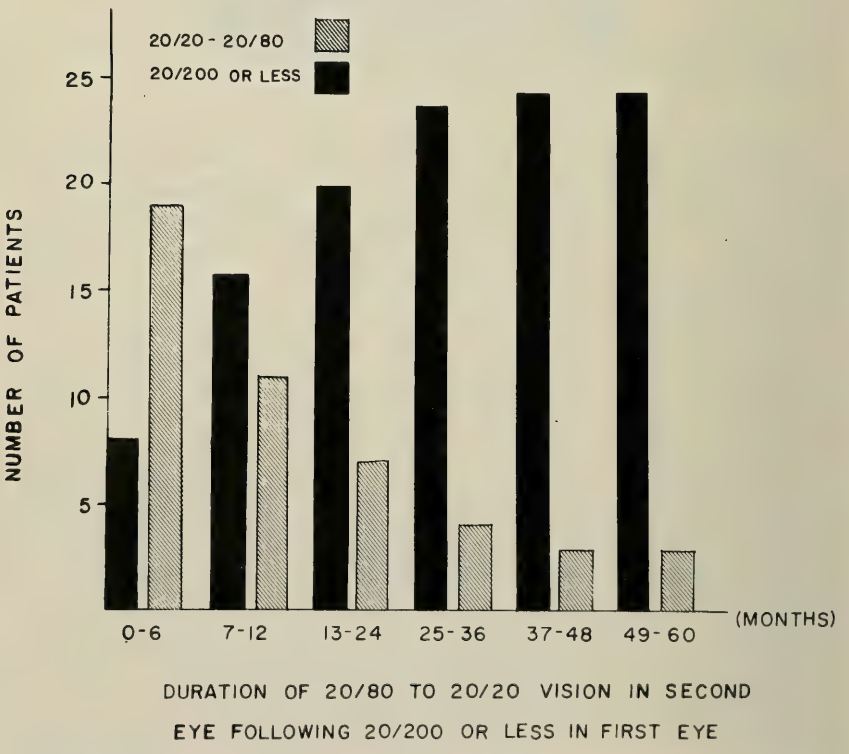

FIGURE 3.—*Duration of useful vision in second eye following severe impairment of first eye.*

first year. The remaining 33⅓ percent of patients whose vision deteriorated lost their vision over a spread of 4 years. This suggests a possible trend, that if the diabetic with severe progressive proliferative retinopathy holds useful vision in his second eye for a full year, his chance of losing it in subsequent years is considerably less. A much larger number of cases must be studied, however, to permit valid statistical treatment of these data for this type patient.

CONCLUSIONS

1. In a small series of patients with advanced diabetic retinopathy who had lost vision to 20/200 or less in 1 eye, the prognosis for maintaining good vision in the second eye was poor. In 89 percent of these patients, the visual acuity of the good eye deteriorated to 20/200 or less during a 5 year period. In 59 percent of these patients, visual loss in the second (better) eye occurred during the first 12 months.

2. On the basis of a previous study, the diabetic who is blind in both eyes has an exceedingly poor prognosis for life, with an average life expectancy of 5.8 years after the onset of severe blindness.

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CHAPTER 9

Summary of Papers on Natural History of Diabetic Retinopathy

MATTHEW D. DAVIS, M.D.

The contributions to this symposium which it is my lot to summarize must be summarized briefly because we are already behind time. I think there are three major things that should be emphasized. The first is the finding, particularly of the Hammersmith group, that capillary closure is an important and early change in diabetic retinopathy. We feel—I think most of the people who have submitted papers on natural history believe—that this is an event which precedes the formation of arteriovenous shunts. The second thing that we probably all agree on is that the new vessels characterizing proliferative diabetic retinopathy go through a cycle of prolifieration and regression. As Mr. Dobree first pointed out very effectively a few years ago, initially the new vessels are bare, without visible accompanying fibrous tissue (Dobree's stage I). After a time fibrous tissue begins to visibly accompany the vessels (stage II), and then in stage III the fibrous tissue really takes center stage as the vessels appear to become less prominent, to regress. It is, I think, essential that we remember this cycle when we evaluate any form of treatment. The third thing that I think we must remember is that when vitreous contraction or contraction of the fibrous tissue associated with the new vessels begins, the eye enters an entirely new phase and vision is now seriously threatened. I believe it is extremely important when we discuss eyes that have been treated to indicate whether they have embarked as yet upon this final phase of vitreous contraction and contraction of fibrous tissue. Now, with these three features of the natural history always before us, we will go on in this next day and a half to discuss treatment.

I have been very much interested in reading the statistics that everyone has submitted. I think there are several important statistics, with which you are all familiar, which should be emphasized. First, the Hammersmith group (ch. 27) shows a clearly significant difference in the outcome of eyes in patients who have had "complete" pituitary ablation versus those who have not. I think we have to admit on the basis of this evidence that pituitary ablation does have some effect on diabetic retinopathy. I think Dr. Okun's series of patients with symmetrical retinopathy in whom one eye was submitted to photocoagulation and the other kept as a control certainly looks as though it will

prove the same thing for photocoagulation (ch. 42). As 1 or 2 more years go by, it probably will prove it more forcefully. Finally, the continuing maintenance of vision in 70 percent of Dr. Field's and associates' large series, even after 2, 3, and more years, becomes more and more difficult to ignore (chs. 19–20).

On the other hand, when we compare some of the treated and control groups, then I find my old doubts returning. I have written a few figures on the blackboard here, if we can move it around a little bit. (Table 1.) These aren't all the figures that could be obtained from the manuscripts you all submitted, but Dr. Myers and I started out with Dr. Beetham's pioneer paper (*1*) and attempted to compare other series with it. We liked his choosing to consider patients that began with 20/40 vision or better and that were followed for at least a year.

The criterion for division of these patients into two groups was: Did they maintain 20/40 or better visual acuity at their most recent visit or did they fall below this? Dr. Beetham's original finding was that 54 percent of 156 patients maintained 20/40 or better vision. The only quibble I have with Dr. Beetham is that I think in the future we should consider eyes rather than patients. I think that the extra problem of the bad eye at the beginning becoming the good eye at the end adds an unnecessary complication. For instance, if we have a patient who is subjected to treatment who starts out with 20/20 in one eye and 20/200 in the other, the eye for which he is treated may go blind while the fellow eye, which perhaps initially had a fresh vitreous hemorrhage, may at the end of a year or more see 20/20. How do we classify such a patient? Is he a success of our treatment? Or do we say he represents a failure, because the eye for which we really treated him is now blind?

At any rate, in table 1 we have selected from the raw data of each investigator listed all eyes with proliferative retinopathy which had an initial vision of 20/40 or better and which were followed for at least 1 year. We have chosen the larger of the various series submitted. As is apparent, there is not a great deal of difference between untreated and treated cases. We might conclude that these figures demonstrate that treatment had no effect, but this might well be an erroneous conclusion, since different criteria may have been used for selection of the patients in the different series. Perhaps the untreated groups contain eyes that had retinopathy so mild that comparable eyes seen by investigators who were carrying out treatment were excluded from their treatment series. Only a generally accepted classification will enable us to cope with this latter possibility. We hope during the course of this meeting to develop such a classification.

TABLE 1.—*Proliferative diabetic retinopathy: eyes with initial visual acuity of 20/40 or better, followed for 1 year or more*

Investigator	Treatment	Number of eyes	Percent with visual acuity 20/40 or better at final visit
Beetham	None	156 [1]	54 [1]
Dobree	do	28	57
Kohner	Improved diabetic control	30	60
Okun and Johnston	None	31	71
University of Wisconsin	do	85	55
Kjellberg et al	Proton beam	45	51
Pearson	Pituitary Ablation	20	45
Dobree	Photocoagulation	19	58
Okun and Johnston	do	70	53
Wetzig	do	50	76

[1] Dr. Beetham submitted patients rather than eyes.

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1. Beetham, W. P.: Visual prognosis of proliferating diabetic retinopathy. Brit. J. Ophthal. 47: 611–619, October 1963.

CHAPTER 10

Summary of Papers on Visual Prognosis

ARNALL PATZ, M.D.

The papers that I will briefly summarize discuss the spontaneous course of visual impairment in patients with diabetic retinopathy. Hopefully, they may be useful as a reference to those papers discussing therapy later in this symposium.

The first is "Diabetic Retinopathy as a Cause of Visual Impairment," by Dr. Caird (ch. 3). This is an excellent review of the prognosis of vision in patients with diabetic retinopathy. In his cases with background retinopathy, younger patients fared far better in a 5-year followup than those, for example, 60 years of age and older. In those patients under 30 years of age at onset of diabetes and with initial good vision, 20/50 or 6/12 or better, the chance of legal blindness occurring (vision less than 20/200) was only 3 percent. These are patients with background retinopathy—whereas in those patients over 60 years of age at the onset of diabetes, the chance of blindness was approximately seven times greater, or 20 percent in a 5-year period of followup.

In general, in patients with mild background retinopathy in his series, those with only microaneursyms fared much better than those patients who had hemorrhages and exudates. Further, those patients with initially impaired vision were much worse off at the end of 5 years than those with initially good vision. Now, by contrast, in Caird's series with proliferative retinopathy he found about 10 times greater deterioration of vision than in those patients who had nonproliferative or background disease. These patients deteriorated to a more severe degree and at a more rapid rate.

In analyzing the prognosis after vitreous hemorrhage, Dr. Caird found that approximately 30 percent were poorer than 20/200 after 1 year. To repeat, approximately one-third of his patients after vitreous hemorrhage had deteriorated to legal blindness within 1 year. And it was significant that in the following 3-year period, only 10 percent additional patients dropped to less than 20/200. In other words, in the 1-year period there was a three times greater number who deteriorated than in the subsequent 3-year period. This prompted Dr. Caird to write:

> This suggests that if blindness does not occur in a year, it is unlikely to do so in the next few years. Perhaps a stable state is reached.

333-611 O—69——9

His data justify the conclusion that if treatment is to be effective, it will need to be applied soon after proliferative changes develop.

In further analyzing this paper as a possible reference to therapeutic reports that will follow in this symposium, it is important to point out that any treatment given patients with proliferative retinopathy and essentially good vision—and I emphasize good vision—must preserve their vision in approximately 60 percent of younger patients over a 5-year period of followup for the therapy to be considered effective.

The other paper that I would like to refer briefly to is that of Drs. Myers and coworkers on the natural course of diabetic retinopathy (ch. 7). It involves a clinical study of 321 eyes followed for 1 year or longer. They have analyzed their data according to their findings at the initial visit using the O'Hare classification.[1] It is interesting that their data are in general agreement with those of Caird on patients with background retinography.

In concluding, I will refer very briefly to the paper of Dr. Berkow (ch. 8) and myself on a small group of patients who had advanced proliferative retinopathy and who had lost vision down to 20/200 or poorer in one eye. This group of patients was followed to see what the natural rate of deterioration would be in the second eye. There were 27 in the group, and 24 at the end of 5 years lost vision in the second eye. Sixteen of these 24 losing vision lost it during the first 12 months, whereas the remaining seven lost their vision during a 4-year period, which is certainly in agreement with the larger series of Dr. Caird, suggesting also that the patient with advanced proliferative disease deteriorates rapidly during an early phase, possibly the first year. And if he passes the first year, then his statistical prognosis is reasonably good.

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[1] O'Hare Classification, p. XXI.

Discussion of Natural History and Visual Prognosis

WILLIAM BEETHAM, M.D., *Moderator*

Dr. Beetham: Somebody asked this question [1]: "In am confused by Dr. Caird's statistics. On the one hand he indicates that the patients with proliferative retinopathy go blind rapidly, within 1 year. On the other hand, 60 percent of those with proliferative retinopathy without visual impairment do well for 5 years. Will he clarify this?"

Dr. Caird: I should point out first that the data on proliferative retinopathy are not mine but Dr. Beetham's (W. P. Beetham, Brit. J. Ophth. 47: 614–619, October 1963). I think the difference is a very simple one. The patients considered with proliferative retinopathy and good vision were as Dr. Beetham presented them. They had proliferative retinopathy, but they had good vision in both eyes, whereas the patients with vitreous hemorrhage were further along the line, having poor vision in at least one eye. There is a gap in time between the first state and the second state. I don't know how long this gap is. Obviously, it varies enormously in individuals. But if you have good vision, the facts are as stated. If you have your first vitreous hemorrhage, they are also as stated. Vitreous hemorrhage, in fact, is much worse for you than having straightforward proliferative retinopathy.

Dr. Beetham: I have been misquoted again. Somebody says: "Dr. Beetham has a paper referring to 10 percent with retained vision after several years in the natural untreated course of the disease." That figure of 10 percent refers to a special group (W. P. Beetham, Brit. J. Ophth. 47: 614–619, October 1963). Every person who quotes it misquotes it. I reported 1,150 consecutive cases of retinitis proliferans who I saw in the office. I took the last vision of each one of them for recording in the paper. I never saw about 500 of them except on that one occasion. Another 200 or 300 were seen three or four times. But for vision purposes I took the last vision. But there was a group of 350 patients who I saw an average of 10 times and over an average period of almost 8 or 10 years. Now, that group of 350 patients is the one that was care-

[1] EDITORS' NOTE.—Certain questions from the audience were relayed to the panel by the moderator.

fully followed, one patient for 22 years and every one of them for, the minimum, I think was 7 or 8 years. And of that 350, 35 reached a quiescent (or an arrested or fibrotic or whatever word you wish to call it) stage where the vascular component or portion stopped and the vessels got small. This fibrous tissue sheen appeared, and vision remained in various states of destruction. Some of them had reasonably good vision. But this 35 (or 10 percent of the 350) which I carefully followed all had some vision. So a group does exist that resolves naturally without anything being done.

Here is another question: "Taking the usual ocular status of patients considered for hypophysectomy (poor vision in one eye, good vision in the second eye), what would you estimate is the 5-year spontaneous course of these patients?"

Dr. Caird: I don't know, because the patients whose figures I have presented have not really fallen into this group. They have been either your patients, Dr. Beetham, who had good vision in good eyes, or the very small group with vitreous hemorrhage. This is why the study of Simonsen, Deckert, and Poulsen is really the best one for comparative purposes. As I understand it, the answer is: 50 percent dead or blind in 5 years.

Dr. Kohner: Fifty percent of 10 patients? Only 10 patients were followed. If you only have 10 patients, you can't say 50 percent of the 10 means very much. We have followed only 10 patients for that time.

Dr. Beetham: "What is the likelihood of a patient with nonproliferative diabetic retinopathy and poor vision obtaining a spontaneous improvement in vision?"

Dr. McMeel: It depends in part on what the cause of loss of vision is.

Dr. Beetham: Let's assume it's background diabetes.

Dr. McMeel: If it's with exudates in the macula, I think the chances of improvement of vision to any significant degree are virtually nil.

Dr. Beetham: And with hemorrhages?

Dr. McMeel: It would be better, but how good I don't know.

Dr. Beetham: Well, you don't get vitreous hemorrhage with the nonproliferative group as a rule, so what other causes could there be for poor vision in these patients?

Dr. McMeel: A continuing edema over a long period of time can depress your macular function also.

Dr. Beetham: "Dr. Davis, do you think all cotton-wool exudates in diabetic retinopathy represent small infarcts, or is it not possible for some of these leaks to occur from a vessel without there being an infarct?"

Dr. Davis: All that we know about the histopathology of cotton-wool exudate suggests that they are infarcts.

Dr. Beetham: Why do they disappear so promptly in some cases and take so long in other cases?

Now, in diabetic pregnancy I have seen them disappear within 4 or 5 days following the termination of pregnancy. Are those due to infarcts?

I would like to know if you think a systemic diuretic influences the absorption of these areas of edema.

Dr. Davis: I don't think a diuretic gets rid of macular edema.

Diabetic soft exudates or cotton-wool spots have a much longer life history than in hypertensives. In fact, all nonhypophysectomized patients showing cotton-wool exudates had these for at least 9 months.

Even when the cotton-wool spot goes, an area of capillary closure exists. We woudn't expect the area of capillary closure to be influenced by diuretics.

Dr. Beetham: But they are, in my experience, with the use of Diuril and its equivalents. I have seen these soft exudates lessen rather rapidly, much more rapidly than you have suggested in your paper—in a matter of weeks, let's say, not months or years as you suggest.

Dr. Kohner: Did you see them develop, or were they there when you first saw them?

Dr. Beetham: They were there in most of the cases that I remember. They were there when I first saw them.

Dr. Kohner: You don't know how long?

Dr. Beetham: But they also had peripheral edema, and the peripheral edema subsided with the diuretics along with the retinal edema.

Dr. Kohner: I find it hard to believe that lesions due to arteriolar occlusion should respond to diuretics.

Certainly, if there is hypertensive retinopathy, which would add to the severity of the diabetic retinopathy, lowering the blood pressure may improve the hypertensive element.

Dr. Beetham: I was trying to correlate peripheral edema with retinal edema.

Dr. Kohner: I don't think that cotton-wool spots are retinal edema.

Dr. Beetham: Well, I always thought they were the same thing, only being a difference of degree and intensity.

Dr. Okun: This is a fairly minor point. Certainly in a cotton-wool spot there is edema, but I think that what Dr. Kohner is getting at is that the reason for the edema is an area of capillary occlusion. Because

of this, there is poor nutrition, and this area of the retina become edematous. It is a superficial retinal edema as compared to the edema that we see in the macula, which is frequently subretinal.

Dr. Becker: Dr. Davis made the point that the first change in diabetic retinopathy was closure of the capillaries. I have read his paper, and I know that this is very much his own thinking as to pathogenesis, but I would like to ask for the documentation that he promised would be forthcoming, and also, to carry it one step further, the mechanism of the capillary closure.

Dr. Davis: I have no documentation for this as an early change. I don't think I said it was the earliest change.

Fluorescein is the best way to demonstrate whether capillary closure precedes shunt vessels or not. The Hammersmith group has the best evidence I have seen, and I would base my opinion on their evidence. I have to call on Dr. Kohner for assistance.

Dr. Kohner: There are really two points here. One is, How do areas of capillary closure come into existence? The second question is, When do the shunt vessels develop?

A collection of microaneurysms, abnormalities of capillaries, is the first thing that happens. Capillary closure is just a more severe abnormality in the capillaries. When the abnormality is really very severe, it also involves arterioles. There is a progression, I think, from microaneurysms to cotton-wool spots, during which time capillary closure develops.

In all patients we studied, even the mildest retinopathies, we did see areas of capillary closure. Patients who had no abnormality on ophthalmoscopy but who had fluorescein studies showed areas of capillary closure surrounded by some microaneurysms.

I can't say all areas of capillary closure develop this way (microaneurysms first), but we have seen this sequence of events now in five patients where we were able to follow this course gradually.

Dr. Davis: I want to make another comment in reply to Dr. Becker. We have the impression we see more areas of presumably obliterated capillaries than could be accounted for by shunt vessels, both in the small amount of human material we have looked at and in the few experimentally diabetic dogs we have studied.

Dr. Kohner: Intra-arterial injections of fluorescein show this at a time when we have no capillary filling. You can see abnormal vessels which are clearly shunt vessels from arterioles, diverting blood into veins before capillaries are filled.

We have quite a number of patients in whom we have seen this sequence of events; namely, capillary closure, with cotton-wool spot

and then without cotton-wool spot. Following the patient for a long time, sometimes a year and longer, finally reveals when the shunt vessel develops.

Occluded capillaries very rarely open. We do see capillaries reopen occasionally or reform. I am not sure exactly what happens. I think they probably reform. But shunt vessels may develop in these areas.

PART III

Relationship of Retinopathy to Metabolic Control

CHAPTER 11

Control of Diabetes and Diabetic Retinopathy

FRANCIS I. CAIRD, D.M., M.R.C.P.

The purpose of the present paper is to review two recent investigations relating to the vexed question of the relationship between control of diabetes and retinopathy. Both are based on ophthalmologists' observations made in the Diabetic Clinic at the Radcliffe Infirmary, Oxford, in the years 1949 to 1965, and both use as the method of assessment of control of diabetes the "glycosuria percentage" (*1*). This is the proportion of urine tests at routine clinic attendances which show glycosuria of 2 percent or more. This proportion is linearly and significantly related to the mean of blood sugars at the same attendances (fig. 1). Each glycosuria percentage represents a wide range of mean blood sugars, but the relationship is the same provided the attendances number five or more, and is unaffected by the age of the patient, and therefore at least by any age-related change in renal threshold for glucose. The glycosuria percentage thus provides a very simple and objective method of ranking groups of diabetics according to their mean blood sugars.

THE FIRST STUDY

Figure 2 shows the relationship between glycosuria percentage and the frequency of retinopathy according to age at diagnosis and duration of diabetes in nearly 3,500 ophthalmologists' observations on nearly 2,000 patients. In patients under 30 at diagnosis of diabetes, those with a glycosuria percentage of 19 percent or less have a lower frequency of retinopathy at all durations of diabetes than those with a higher glycosuria percentage, but none of the differences between pairs of groups are significant by themselves. It is however possible to show by probit analysis that the two curves are significantly different. The mean duration of diabetes associated with a 50 percent chance of retinopathy is significantly shorter (12.9 ± 0.6 years) in those with the higher glycosuria percentage than in those with the lower (15.4 ± 1.0 years). It is thus as though the lower percentage were associated with a postponement by 2.5 years of the development of retinopathy.

In patients between 30 and 60 at the diagnosis of diabetes, the frequency of retinopathy is significantly lower in those with the lower

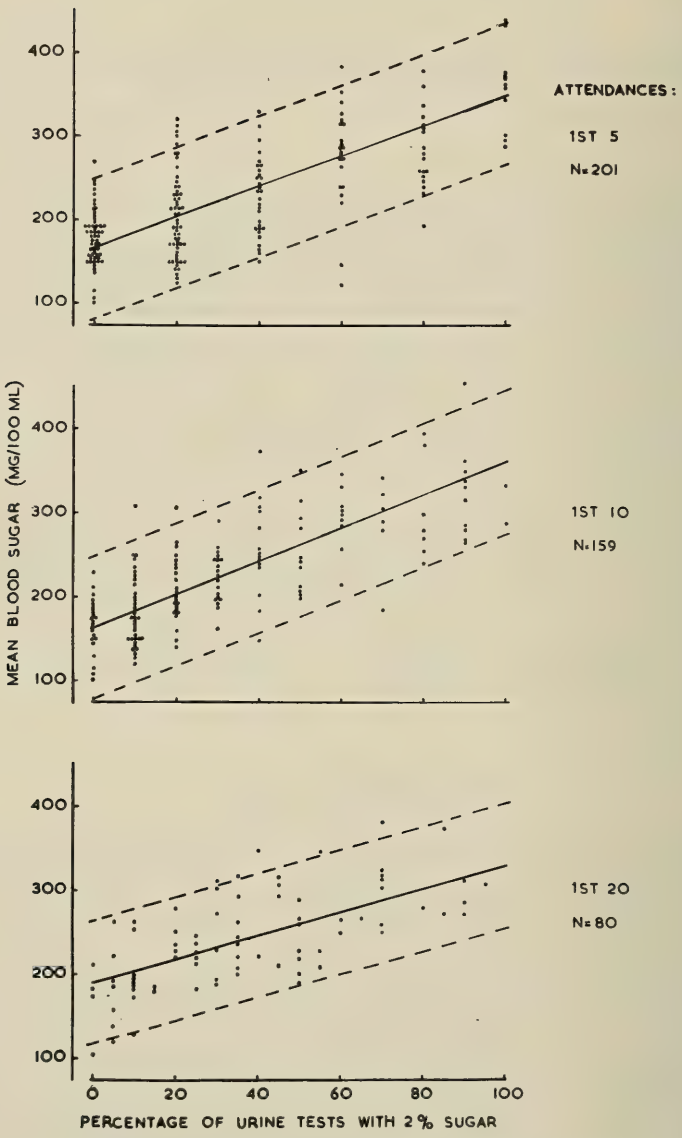

FIGURE 1.—*Relationship between glycosuria percentage (abscissa) and mean of blood sugars at clinic attendances (ordinate) for first 5, 10, and 20 attendances.*

glycosuria percentage for duration of 10 to 14, 15 to 19, and 20 to 24 years. There are no significant differences in those over 60 at diagnosis.

Table 1 shows the chances of development of retinopathy in patients with serial observations and initially normal fundi. These chances are lower in those with the lower glycosuria percentage in all

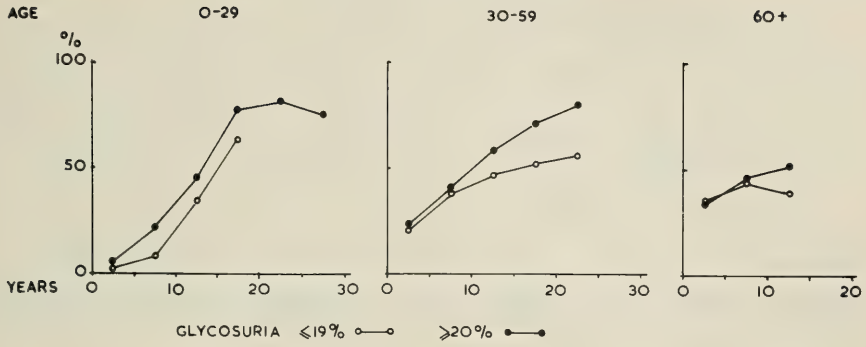

FIGURE 2.—*Frequency of retinopathy (ordinates) in ophthalmologists' observations in relation to duration of diabetes (abscissae). Age: age at diagnosis of diabetes. Open circles: glycosuria percentage 19 percent or less; closed circles: glycosuria percentage 20 percent or more.* (2)

but one of the nine pairs of groups whose initial observation was within 5 years of diagnosis of diabetes; the differences are significant in five of the nine pairs. There are no significant differences when the initial observation was over 5 years from diagnosis.

Table 2 shows that the chances of progression and regression of retinopathy are unrelated to the glycosuria percentage. This applies both to patients with only microaneurysms, and to those with more severe "background" retinopathy, retinal hemorrhages and/or exudates. Data on patients under 30 and over 60 at diagnosis are too few to reproduce, and we have no adequate data on glycosuria percentage and the course of proliferative retinopathy.

Patients with the lower glycosuria percentage do not differ from those with the higher percentage in respect of sex ratio, family history of diabetes, parity at diagnosis of diabetes, or frequency of admission with diabetic ketosis. Among those over 30 at diagnosis, more

TABLE 1.—*"Glycosuria percentage" and chances of development of retinopathy in patients with normal fundi*

Age at diagnosis of diabetes	Duration of diabetes at 1st observation (years)	"Glycosuria percentage"	Interval after 1st observation (years)			
			0–4	5–9	10 plus	All
0 to 29	0 to 4	⩽19	0/7	2/9=18% [1]	3/9	5/25=20%
		⩾20	4/15=27%	12/21=57% [1]	10/14=71%	26/50=52%
30 to 59	do	⩽19	14/55=25% [1]	38/98=39% [1]	5/29=17% [2]	57/182=31%
		⩾20	18/34=53% [1]	32/57=57% [1]	15/24=63% [2]	65/115=57%
	5 to 9	⩽19	12/20=60%	3/11=27%	1/6	16/37=43%
		⩾20	3/11=27%	7/14=50%	1/5	11/30=37%
60 plus	0 to 4	⩽19	21/47=45%	17/55=31% [1]	1/12=9%	39/119=34%
		⩾20	7/19=37%	8/11=72% [1]	1/5	16/35=46%

[1] Difference within pair significant at 5 percent level.
[2] Difference within pair significant at 1 percent level.

TABLE 2.—*"Glycosuria percentage" and chances of progression and regression of retinopathy*

	Age at diagnosis of diabetes	"Glycosuria percentage"	Interval after 1st observation (years)			
			Progression		Regression	
			0–4	5–9	0–4	5–9
Microaneurysms alone.	30 to 59	≤19	23/35=66%	2/13=16%	9/35=26%	2/13=16%
		≥20	8/12=67%	1/3	3/12=25%	0/3
Hemorrhages and/or exudates.	30 to 59	≤19	5/33=15%	6/32=19%	9/33=27%	6/32=19%
		≥20	0/28=0%	4/23=17%	12/28=43%	2/23=9%

of those with the lower glycosuria percentage were treated with diet alone or with oral hypoglycemic agents, and fewer with insulin. This is not unexpected, since the greater the glycosuria or hyperglycemia, the more likely is a patient to be treated with insulin.

This study therefore suggests that better control of diabetes, as assessed by the glycosuria percentage, is associated with a lower frequency of retinopathy, at least in patients under 60 at diagnosis, and with reduction in chances of development of retinopathy if better control starts within 5 years of diagnosis of diabetes. By contrast, it is not possible to demonstrate any effect of better control on the chances of progression or regression of established retinopathy, however early.

THE SECOND STUDY (*3*)

This was designed to examine the relationship between glycosuria percentage and the frequency of retinopathy in greater detail, and also to investigate the suggestion made by Constam (*4*) and supported by some evidence from the previous study, that it may be in the first few years of diabetes that the effects of control in reducing the frequency of complications is most critical.

Two hundred and ninety-nine patients were studied; all had attended the clinic from within 6 months of diagnosis of diabetes, all had an ophthalmic observation 10 to 14 years after diagnosis, all had attended the clinic at least 10 times (the mean number of attendances was 44). Table 3 shows the sex and age at diagnosis of the patients.

Table 4 and figures 3 and 4 show the relationship between the frequency of retinopathy 10 to 14 years after diagnosis and the glycosuria percentage in three periods: the whole period of 10 to 14 years, a first period of the first 3 to 7 years after diagnosis (average 4.8), and

TABLE 3.—*Age and sex of patients in 2nd study*

Age at diagnosis of diabetes	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	Total
Men	2	12	11	14	23	28	19	1	110
Women	0	10	13	13	31	74	47	1	189
Total	2	22	24	27	54	102	66	2	299

TABLE 4.—*Correlation between glycosuria percentage and frequency of retinopathy 10 to 14 years after diagnosis of diabetes*

Glycosuria percentage	0	1–9	10–19	20–29	30–39	40–49	50–59	60+	Correlation coefficient	P
Whole period	5/23	24/70	33/68	21/42	18/30	15/29	13/19	13/18	0.91	<0.01
Percent	22	34	48	50	60	52	68	72		
1st period	8/31	27/72	25/57	20/39	9/20	20/30	14/21	23/29	0.83	<0.02
Percent	26	38	44	51	45	67	67	79		
2d period	22/74	24/52	26/42	15/36	21/38	13/20	9/15	11/22	0.47	0.90
Percent	30	46	62	42	55	65	56	50		

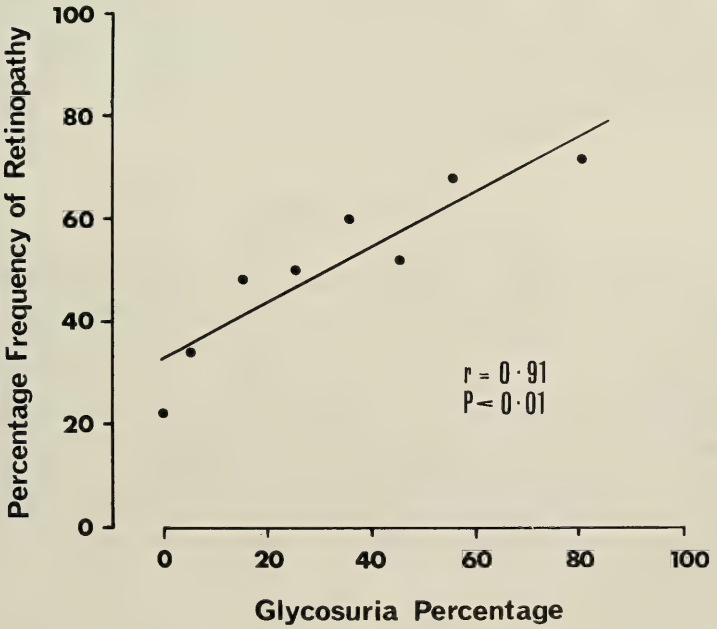

FIGURE 3.—*Correlation between frequency of retinopathy 10 to 14 years after diagnosis of diabetes and glycosuria percentage in whole period.* (3) (*See table 4.*)

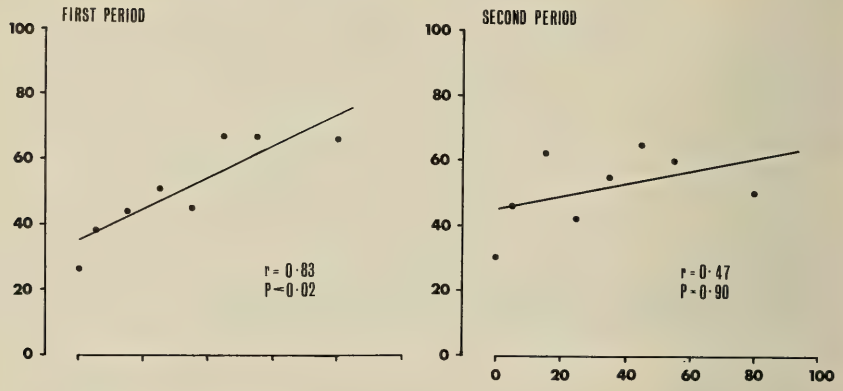

FIGURE 4.—*Correlation between frequency of retinopathy 10 to 14 years after diagnosis of diabetes (ordinates) and glycosuria percentage in first period (upper graph) and second period (lower graph) (abscissae). (3) (See table 4.)*

a second subsequent period of average length 6.2 years. A highly significant correlation is shown between the frequency of retinopathy and the glycosuria percentage in the whole period, and in the first but not the second period. This correlation can be shown to be independent of age.

The second study thus confirms the first in showing that it is possible to demonstrate a clear and significant relationship between better control of diabetes and the frequency of retinopathy. It also confirms Constam's most interesting suggestion that the first few years of diabetes are the most important in this relationship.

CONCLUSIONS

These studies suggest that close control of diabetes reduces the frequency of retinopathy most if it is applied in the first few years after diagnosis, and has less effect as the years pass, until when frank retinopathy, however slight, is present, it has no effect at all. One interesting consequence of this view is that it will prove difficult or impossible to show any relationship between control and retinopathy in an investigation in which a considerable proportion of patients were entered after having had diabetes for some years (*5*). This may well be one reason why this vital problem has remained in dispute for so long.

Acknowledgements

Figure 1 is reproduced with permission from "Diabetes" and the American Diabetes Association; tables 1 and 2, the Quarterly Journal of Medicine; and tables 3 and 4 and figures 3 and 4, Messrs. Blackwells Scientific Publications.

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333–611 O—69——10

CHAPTER 12

The Control of Diabetes Mellitus and the Progression of Retinopathy

HARVEY C. KNOWLES, JR., M.D.

The purpose in treatment of diabetes mellitus is to achieve normal health and activity for the patient. The general approaches to this consist of institution of a regulated plan of eating, administration of insulin or oral blood sugar lowering drugs, if needed, and provision of supporting treatment to include a wide range of measures. The greatest effort is directed toward return to normal of the abnormalities caused by insulin insufficiency. This return toward normal is referred to herein as control of diabetes. The point in question is whether or not a relation exists between degree or success of control, and the rate of clinical appearance of retinopathy.

In the past 35 years several hundred publications dealing with this question have appeared both here and abroad. The majority of authors or groups of authors expressed the opinion that a significant relation exists, and that the better control, as defined above, the less would be the incidence of retinopathy. This view was and is based on the results of prevalence studies in which the degree of retinopathy was related to estimates of control, on animal studies in which alloxan diabetes was reported to be followed by retinopathy and glomerulosclerosis, on the fact that plasma lipids are elevated in uncontrolled diabetes and this elevation is related to large vessel sclerosis, and finally on the general impression that patients who have less retinopathy seem to have had better control of their diabetes. The point of view that control is beneficial has been advanced in this country by Marble (*1*), Hardin (*2*), and Duncan (*3*); in England by Dunlop et al. (*4*) and Burditt (*5*); and in Switzerland by Constam (*6*).

A smaller number of interested physicians, originally consisting of Dolger (*7*) and Tolstoi (*8*) in New York, Mirsky (*9*) in Pittsburgh, and Lichtenstein (*10*) in Stockholm questioned whether control of diabetes had any relation at all to the course of vascular disease. The present writer does not deny that a relation may exist but is of the view that proof of such is not yet available.

To begin with, the cause of retinopathy is unknown. The lesions are varied in pathologic nature, and it is not certain if common mechanisms are concerned in the pathogenesis. It seems clear now that exudates are related in part to lipid intake and plasma lipids, since

they will regress on a low fat diet. But it is not known if lipid metabolism is related to aneurysm formation and neovascularization. For that matter, these two lesions may have entirely different reasons for development. Influencing variables proposed to hasten retinopathy have included genetic, hormonal, nutritional, and even psychic factors. In fact, there is hardly any stress that man has been faced with that hasn't been incriminated. The influence receiving the most attention remains control of diabetes, however.

The hypothesis that control of diabetes will affect favorably the course of retinopathy must assume that insulin insufficiency in itself is influential. The observations of Bloodworth (*11*, *12*) of microangiopathy in "alloxanized" dogs, and the appearance of clinical retinopathy and glomerulosclerosis in patients with pancreatic diabetes lend support to this thesis. Unfortunately, these cases are few, and the existence of genetic diabetes cannot always be excluded. The demonstration of microangiopathy in pancreatic diabetes in frequency beyond that expected from randomized distribution of genetic diabetes would be of the greatest importance to establish a relation of vascular disease to pancreatic failure.

Studies relating control of diabetes to the course of retinopathy have not always been satisfactory. Often they have suffered from deficiencies in experimental design, from inadequacies of measurements of variables, and sometimes from failure to apply appropriate means to test data. In most instances frequencies expressed were of prevalence rather than incidence. Patients were recalled for observation, examination was made for presence or absence of retinopathy, and retrospective estimates made of diabetic control. Records were examined for blood sugar levels which might have been determined at unplanned times or for statements as to whether or not the patient was adhering to a prescribed regimen. Prospectivity of observation was not employed. Rarely was the error encountered in measuring response variables taken into account.

Perhaps the greatest difficulty of all lay in estimating control of diabetes. Herein all studies faltered, for it was impossible to determine with surety what the day-to-day course of blood sugar levels of patients was. Instead, it was necessary to rely on patients' urine records and blood sugar levels determined at outpatient visits. Many workers realized the difficulty in evaluating glycemia and fell back on measures such as diet adherence, weight change, patient motivation, and even the impression of the physician. To resolve the problem of control of diabetes and its relation to vascular disease will require a carefully designed prospective study with satisfactory measures of variables and correct interpretation of the data.

The above is not to be taken to indicate that a beneficial effect of control on retinopathy may not exist. Rather, this writer is of the view that proof is not yet available. Studies have been published showing that the incidence of retinopathy was little different in groups treated with liberal regimen from that in groups given rigid treatment for tighter control. As a result, questions arise which, to this writer, cannot be answered at this time.

First, does diabetes uncontrolled to the point of symptoms hasten the course of retinopathy? This writer knows of no observations substantiating this. Second, why do diabetic patients treated with liberal regimen have retinopathy in frequency comparable to those treated with strict regimen? If a strict regimen does have influence, then those so treated do not adhere to it, or its influence may be small so as to be overshadowed by other determinants unevaluated as yet. If a strict regimen leading to better control is beneficial, can it be applied in this country today? Physician time for education is limited, and motivation in patients must be developed.

The most significant point is that retinopathy occurs too commonly in patients undergoing today's treatment of diabetes. Otherwise there would not be need for this conference. If control is of benefit, then better means to apply it must be found. But it appears to this writer that it is more urgent to develop other approaches to the prevention and management of retinopathy.

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CHAPTER 13

The Effect of Diabetic Control on Diabetic Retinopathy [1]

EVA M. KOHNER, B. Sc., M.B., M.R.C.P.
T. RUSSELL FRASER, M.C., F.R.C.P.
GRAHAM F. JOPLIN, Ph. D., M.R.C.P.
NIGEL W. OAKLEY, M.B., Ch. B., M.R.C.P.

Of all the late complications of diabetes mellitus, retinopathy is the most distressing and often the most disabling one. Many treatments have been tried to avert the threat of blindness and to slow down the progress of the retinopathy. Some of the treatments, such as rutin, vitamin B_{12} and anabolic steroids have been shown to be of no value; while others such as photocoagulation and pituitary ablation are still experimental.

The exact place of "good diabetic control" in the treatment of diabetic retinopathy has not been established. Many authors, including Keiding et al. (*1*), Constam (*2*), Skouby (*3*), Kornerup (*4*), and Schlesinger et al. (*5*) have found that good control of diabetes may delay or even prevent the onset of vascular complications. Hardin et al. (*6*) found in addition, that not only the incidence, but also the severity of the retinopathy correlated well with the degree of diabetic control, those being well controlled having the milder lesions. On the other hand Kornerup (*4*) found that strict control did not prevent the development of proliferative lesions, and Schlesinger et al. (*5*) found no good evidence for the influence of good control on established retinal lesions.

The present work is a preliminary report of a prospective study on the progress of established diabetic retinopathy related to diabetic control in a group of 104 patients most of whom were studied between 1965 and 1968 at the Hammersmith Hospital, London.

PATIENTS AND METHODS

1. *Patients studied.*—For inclusion into the study the patient's age had to be between 15 and 70 years and he had to have at least one eye photographable. The patients studied came from two sources: (1)

[1] See appendix A for raw data on individual patients.

The Royal Postgraduate Medical School and Hammersmith Hospital, Du Cane Road, London W. 12.

patients without visual symptoms related to the retinopathy (74), but who were found to have retinopathy on a diabetic clinic survey carried out between October and December 1965. (To this category were added similar symptomless patients with retinopathy, who attended the clinic at a later date and were followed for at least 6 months.) (2) patients who had visual symptoms (30), most of whom were referred for consideration for pituitary ablation by outside doctors. Some of these patients were randomly selected to become "controls" to the yttrium implanted patients; two had declined implant when this was first advised. Others were judged to be unsuitable for pituitary implantation because of too mild or too severe retinopathy, or because of general medical contraindications.

In all, 104 patients having 199 photographable eyes were included in the study. The mean followup period was 22.9 months. In three of these patients there was inadequate data on diabetic control and they were therefore excluded from the analysis relating progression of retinopathy to diabetic control. In one patient visual acuity could be analyzed only, as his only eye became unphotographable before the first follow up.

2. *Assessment of diabetic control.*—An attempt was made in all patients to achieve optimum diabetic control by means of diet only or diet and hypoglycemic agents. Where possible, patients requiring over 40 units of insulin daily were changed to twice daily soluble (regular) and isophane (NPH) insulin, unless previous control was judged to be good. The threshold for glycosuria was determined in 51 patients. In all of the others threshold determination was attempted, but proved unsuccessful. The threshold for glycosuria was determined from a series of simultaneous fasting capillary blood and urine samples, the threshold being the level of blood sugar at which glycosuria became evident. Clinitest (Ames) tablets were used for urine testing, and the Technicon ferricyanide autoanalyzer method was used for blood sugar determination.

The patients were taught to test their own urine and were asked to test at least twice daily premeal in alternate weeks. Patients requiring diet only or diet and oral hypoglycemic agents were allowed one daily test after an initial 6 months of more frequent testing if all their home tests were blue. Patients with low threshold were also not required to test so frequently.

Additional blood sugar determinations were made fasting and premeal. Most patients had a blood sugar determination at each clinic attendance; in any case at least six blood sugar figures were available for each patient over the 2-year period. Forty-six of the 104 patients were admitted for investigation or for medical reasons and blood

sugars were then taken repeatedly over 24-hour periods, usually premeal.

Patients were divided into four categories of diabetic control on the basis of all these blood sugar and urine test results.

(1) Very good control: Urine tests, at least 60 percent blue or a mean figure for the urine tests over the period of study of less than 0.1 percent; and blood tests, fasting blood sugar consistently under 150 mg. percent.

(2) Good control: Urine tests, as for very good control; blood tests, some fasting blood sugar estimations over 150 mg. percent.

(3) Fair control: Urine tests, less than 60 percent of tests blue, or a mean of all urine tests between 0.1 and 0.5 percent; and blood tests, mainly under 300 mg. percent.

(4) Poor control: Urine tests, frequently 1 percent or more glycosuria, or a mean urine test figure of over 0.5 percent; or blood tests, over 300 mg. percent premeal on several occasions.

In addition if the patients were markedly overweight and failed to reduce, or actually gained weight against medical advice they were placed in a category one worse than they would have been on other test results. Similarly, frequent hypoglycemic episodes precluded inclusion into the "very good" and "good" control groups. In patients with low thresholds, thresholds over 220 mg. percent and those who refused to check the urine regularly, blood tests alone were used to test the degree of control achieved.

3. *Assessment of eyes.*—The pupils were dilated with both 0.5 percent mydrilate and 10 percent phenylephrine eye drops. Retinal photographs were taken using a Zeiss fundus camera and Kodachrome II film processed commercialy. Pictures were taken at the time of entry into the trial and approximately yearly thereafter (range of interval was 6 to 15 months). Three standard areas were photographed in each patient: superior temporal, inferior temporal including the macula, and nasal including the disc. Other areas were photographed when of special interest. On at least one occasion most of the retina was surveyed by retinal photographs. The mean "1-year followup" was 11.4 months and the mean "latest followup" was 27.1 months.

For grading the eyes, the Hammersmith grading system as described by Oakley et al. (7) was used, grading individually for each retinopathy feature and taking the mean of three fields studied in any one eye as the mean for the feature for that eye. Patients or eyes who became unavailable for more than one set of retinal photographs were excluded from the study.

Visual acuity: This was recorded by using a standard illuminated Snellen chart at 6 meters. Patients with visual symptoms were re-

fracted, while those without used their own glasses or a pinhole when necessary. The visual acuity was converted to numerical scale as described by Oakley et al. (7) with the exception that 6/6 and 6/5 were combined, and both were graded as 1.

RESULTS

The distribution of the patients according to age of onset and duration of diabetes at the time of the study is shown in table I. The table indicates that the duration of diabetes was longer in the juvenile onset diabetics than in the other groups. Since no patient over 70 years was included in the study, there was no patient whose diabetes was diagnosed after the age of 50 with a duration of over 20 years.

Table II shows the duration of diabetes at the time retinopathy was first diagnosed related to the age of onset. As expected, only a few patients with juvenile onset diabetes had retinopathy detected within 10 years of diabetes diagnosis. On the other hand, most of the patients whose diabetes was recognized after the age of 50, had some features of diabetic retinopathy within the first 5 years of this recognition. Some had visual symptoms at the time when diabetes was diagnosed.

The distribution of patients according to category of diabetic control is illustrated in table III. Though the number of patients is comparable in the different control groups, the age distribution is totally different. This alone would be expected to influence the prognosis of

TABLE I.—*Duration of diabetes at time of study*

Age of onset	Duration				
	0–5	6–10	11–20	Over 20	Total
Up to 29	0	3	14	16	33
30 to 49	5	10	16	6	37
Over 50	17	7	9	0	33
Total	22	20	39	22	103

TABLE II.—*Duration of diabetes when retinopathy diagnosed*

Age of onset	Duration				
	0–5	6–10	11–20	Over 20	Total
Up to 29	0	7	17	13	37
30 to 49	13	8	18	0	39
Over 50	20	5	2	0	27
Total	33	20	37	13	103

TABLE III.—*Age of onset of diabetes and diabetic control*

Age of onset	Control group				Total
	Very good	Good	Fair	Poor	
Under 30	2	6	14	11	33
30 to 50	8	8	13	11	40
Over 50	9	10	6	3	28
Total	19	24	33	25	101

the retinopathy. Only eight out of 33 patients (24.2 percent) whose diabetes started before the age of 30 had "very good" or "good" control, while 19 out of the 27 patients (70.3 percent) with late onset of diabetes fell into these categories.

The difference between the different categories of control is further emphasized in Table IV, which shows that only two insulin-requiring diabetics reached "very good" control, while only two tablet-requiring patients fell into the "poor" control category.

The effect of diabetic control on the individual features of diabetic retinopathy is shown in Tables V–VIII.

Microaneurysms and hemorrhages: Microaneurysms and hemorrhages (MA and H) (table V) tended to deteriorate both at the 1 year and the latest assessments when all eyes were considered together. Taking the individual control groups separately, those with "very good" control showed an insignificant improvement, while all others deteriorated. The deterioration was most significant in those with "poor" control. This result is the more important as the initial mean grading of the categories with "very good" control was significantly worse than that of the "good" and "fair" control group ($p=.01$ and $p=.007$). All other groups when compared with each other had similar initial gradings. Comparing the control groups with each other, those with "very good" control fared better than each of the others at both the one year and the latest assessments. There was no significant difference between the other groups.

Exudates: Patients with "very good" and "good" control showed deterioration in hard exudate grading, both at the one year and the

TABLE IV.—*Treatment of diabetes in the different control groups*

Treatment	Very good	Good	Fair	Poor	Total
B.D. insulin	2	8	23	19	52
Daily insulin	0	3	3	4	10
Tablets	13	9	6	2	30
Diet only	4	3	1	0	8
Total					101

TABLE V.—*Effect of diabetic control on microaneurysms and hemorrhages**

[Paired T-test has been used. Positive (+) difference = worsening. Negative (−) difference = improvement]

Control category	Initial (mean ± S.E.)	1 Year (mean ± S.E.)	Difference between initial and 1 year (mean ± S.E. of difference)	Initial (mean ± S.E.)	Latest (mean ± S.E.)	Difference between initial and latest (mean ± S.E. of difference)
All eyes	1.33±0.07	1.46±0.07	[1] +0.12±0.04	1.33±0.07	1.53±0.07	[1] +0.20±0.06
Very good control	1.80±0.25	1.69±0.19	−0.11±0.14	1.44±0.21	1.41±0.16	−0.03±0.12
Good control	1.15±0.14	1.31±0.14	[2] +0.19±0.07	1.03±0.13	1.32±0.13	[1] +0.29±0.08
Fair control	1.23±0.11	1.45±0.12	[2] +0.22±0.08	1.03±0.11	1.25±0.12	[2] +0.22±0.11
Poor control	1.33±0.14	1.53±0.15	[1] +0.19±0.07	1.06±0.13	1.41±0.14	[1] +0.35±0.10

[1] P=<0.01.
[2] P=0.05–0.01.
* All numbers in tables V through VIII refer to the Hammersmith classification described in reference 7.

TABLE VI.—*Effect of diabetic control on exudates*

[Paired T-test has been used. Positive (+) difference = worsening. Negative (−) difference = improvement]

Control category	Initial (mean ± S.E.)	1 Year (mean ± S.E.)	Difference between initial and 1 year (mean ± S.E. of difference)	Initial (mean ± S.E.)	Latest (mean ± S.E.)	Difference between initial and latest. (mean ± S.E. of difference)
All eyes	0.77±0.07	0.85±0.06	0.07±0.04	0.72±0.07	0.70±0.05	0.09±0.06
Very good control	0.76±0.13	1.01±0.15	[1] +0.25±0.12	0.85±0.15	1.11±0.17	[1] +0.25±0.10
Good control	0.69±0.12	0.84±0.14	[1] +0.15±0.07	0.58±0.10	0.65±0.10	+0.07±0.10
Fair control	0.58±0.11	0.59±0.07	+0.09±0.07	0.58±0.13	0.56±0.78	−0.03±0.13
Poor control	1.11±0.15	1.03±0.13	−0.08±0.07	0.95±0.18	0.98±0.14	+0.03±0.09

[1] P=0.05–0.01.

latest assessments (table VI). There was no significant difference in the "fair" and "poor" control groups. This apparently paradoxical result is probably explained by the fact that hard exudates are related more to age, or age of onset of diabetes than diabetic control.

New vessels: New vessels deteriorated when all eyes were considered together (table VII). While in the "very good" and "fair" control category there was no real change, deterioration occurred in those with "good" control and was marked in those with "poor" control. The initial grading was similar for all groups. The relative benefit of "fair" control needs explanation. This group includes two patients who show an apparent improvement from 3.0 to 0.0 and 2.7 to 1.7 in one eye each (D.R., Rt. eye and E.S., Lt. eye).[1] In these two patients the new vessels progressed to retinitis proliferans, the new vessels themselves disappearing. A third patient, S.H., showed initial grading of 3.0 in both eyes. Her control at the time was extremely poor and she had lipemia retinalis. Very good diabetic control was achieved during the next few months, but this later deteriorated. During the period of "very good"

[1] See Appendix A.

TABLE VII.—*Effect of diabetic control on new vessels*

[Paired T-test has been used. Positive (+) difference=worsening. Negative (−) difference=improvement]

Control category	Initial (mean ± S.E.)	1 Year (mean ± S.E.)	Difference between initial and 1 year (mean ± S.E. of difference)	Initial (mean ± S.E.)	Latest (mean ± S.E.)	Difference between initial and final (mean ± S.E. of difference)
All eyes	0.24±0.05	0.33±0.05	[1] 0.08±0.04	0.15±0.03	0.25±0.04	[2] 0.09±0.04
Very good control	0.59±0.23	0.63±0.17	+0.04±0.17	0.21±0.08	0.35±0.13	+0.15±0.16
Good control	0.31±0.11	0.58±0.15	[2] +0.27±0.11	0.19±0.10	0.78±0.21	+0.59±0.19
Fair control	0.52±0.17	0.43±0.10	−0.09±0.80	0.49±0.18	0.39±0.11	−0.12±0.18
Poor control	0.55±0.19	1.15±0.27	+0.59±0.19	0.29±0.12	0.69±0.18	+0.39±0.16

[1] P=<0.01.
[2] P=0.05=0.01.

control her eyes improved and remained good, though she failed to keep up her good diabetic control. (This patient was reported by Dollery and Oakley in 1965) (*8*). These patients contribute a mean of 1.7 at 1 year, and a mean of 3.0 at the latest assessment, and can account at least in part for the result.

Retinitis proliferans: There was a significant overall deterioration in retinitis proliferans (table VIII) at the 1 year and latest assessments. Deterioration occurred in all groups, but the numbers were too small for assessment of individual control categories separately.

Visual acuity: Visual acuity was assessed only at the first and last examination. Taking all patients, there was a highly significant deterioration (p.<0.0001) of just over half a line during the mean period of followup. In patients with new vessels it was almost a full line. (0.806). The deterioration of patients with visual symptoms and those who were followed for more than 1 year was over two lines (2.067); all but three of this group had new vessels.

Influence of age of onset of diabetes, blood urea and blood pressure: It was thought to be of interest to study factors which may affect the formation of new vessels, as prognostically they are the most sinister

TABLE VIII.—*Effect of diabetic control on retinitis proliferans*

Paired T-test has been used. Positive (+) difference=worsening. Negative (−) difference=improvement]

Control category	Initial (mean ± S.E.)	1 Year (mean ± S.E.)	Difference between initial and 1 year (mean ± S.E. of difference)	Initial (mean ± S.E.)	Latest (mean ± S.E.)	Difference between initial and latest. (mean ± S.E. of difference)
All eyes	0.85±0.19	1.35±0.24	[2] +0.49±0.15	0.79±0.24	1.19±0.23	[1] +0.40±0.09
Very good control	1.10±0.46	1.67±0.39	+0.57±0.24			[1] 0.33±0.10
Good control	0.83±0.39	0.93±0.43	+0.10±0.07			
Fair and poor control	0.75±0.30	1.43±0.44	[2] +0.69±0.35			[2] +0.79±0.27

[1] P=<0.01.
[2] P=0.05-1.01.

TABLE IX.—*Blood urea and type of retinopathy*

Blood urea	Type of Tetinopathy		Difference
	Background	Proliferative	
Initial (mean ± S.E.)	37.21±1.195	45.89±3.642	[1] 8.68
Final (mean ± S.E.)	37.38±1.234	57.97±9.726	[1] 20.59

[1] P=<0.01.

feature of diabetic retinopathy together with retinitis proliferans. As in other series it was found that the onset of diabetes in those with proliferating retinopathy (new vessels and retinitis proliferans) was at a younger age than in those who had only background retinopathy. The mean age at diagnosis of diabetes for those with proliferating retinopathy was 32.2 years in comparison to 42.7 years for those with background retinopathy (p=0.006). The duration of diabetes however was comparable in the two groups (13.6 and 14 years respectively). Both the initial and the final blood urea estimations were significantly higher in patients with new vessel systems compared with those who only had background retinopathy (table IX). Diastolic blood pressure did not appear to be significantly different in the two groups 86.4±1.83 and 90.1±2.28). This may be explained by the fact that those with diastolic blood pressure readings of over 100 mm. Hg. were treated with hypotensive agents. Of the five patients who died during the period of study and who were followed for over 6 months, four had raised blood pressure and three also had raised blood urea when first entering the series. The fifth patient who had rheumatic heart disease died from bronchopneumonia. Neither retinal hemorrhages nor new vessel systems correlated with diastolic blood pressure readings; changes in blood pressure readings did not correlate with changes in new vessel or hemorrhage gradings.

DISCUSSION

The results show that microaneurysms and hemorrhages remained unchanged only in patients with very good control, while in all other groups they deteriorated. As regards new vessels, a similar outcome was observed (leaving aside the "fair" control group). Worsening of exudates occurred in spite of "very good" control and "good" control but no change was seen in the others.

Although the patients with "very good" control were mostly adult-onset diabetics, nevertheless this group seemed to have the best prognosis. This is contrary to findings of Burditt et al. (*9*) who noted that

the chances of progression of retinopathy increased while the chances of regression decreased with advancing age at diagnosis of the diabetes. However some of the differences between the results can be accounted for by the fact that Burditt et al. considered hemorrhages and exudates together while our study indicates that they progress at different rates. Also, the influence of diabetic control was not considered in the progression of lesions in their patients.

The allocation of the patients to the different categories of diabetic control in this series was according to test results during the period of study. It did not include any reference to previous diabetic control. An attempt was made to achieve optimum control in all patients and considerable improvement was achieved in some. In the 19 "very good control" patients, change in management of diabetes had been necessary in only three patients (two were insulin requiring); while in the "fair control" category, 16 out of 33 (48.5 percent) had had their treatment altered at their entry into the trial and in all of these control improved, sometimes from previous very poor control. Some improvement in control was also noted in nine out of 25 patients with "poor" control (36 percent). Some remissions in all retinopathy features occurred at times irrespective of change in diabetic control, but the most striking remissions of both new vessels and hemorrhages, such as reported by Davis (*10*) occurred in those whose control improved most.

Motivation of the patients (such as by visual symptoms), a fuller understanding of the diabetic management, and intelligence contributed to improvement in control. This is similar to what was noted by Williams et al. (*11*). Lack of more marked improvement in diabetic control in at least 8 patients with fair and poor control was due to the presence of other diabetic complications such as affection of the gastrointestinal tract, renal involvement or coronary artery disease. In only four patients was there a lack of cooperation and it was these four patients who had conspicuously worse diabetic control than the others.

Although these results indicate that perseverance in good diabetic control is worthwhile even in established diabetic retinopathy, full assessment of its value in preventing progression of lesions will have to await a longer period of follow up.

SUMMARY

1. One hundred four patients with established diabetic retinopathy were followed for a mean period of 22.9 months. The progression of the individual features of the retinopathy was related to the degree of diabetic control achieved.

2. Only "very good" diabetic control seemed to protect patients from worsening of microaneurysms, hemorrhages and new vessels. Worsening of exudates occurred in the "very good" and "good" control groups while retinitis proliferans deteriorated irrespective of diabetic control.

3. It is concluded that "very good" control of diabetes is of value even in established diabetic retinopathy but the full evaluation of its role will have to await longer followup period.

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CHAPTER 14

Summary of Papers on Relationship of Retinopathy to Metabolic Control

HARVEY C. KNOWLES, JR., M.D.

There are few topics in the field of internal medicine which have been debated as much as whether or not control of diabetes influences the course of vascular disease. In the papers prepared for this symposium there are only three which deal with the problem of control—my own (ch. 12), one by Dr. Caird from the Radcliffe Infirmary (ch. 11), and one by Dr. Kohner et al. from Hammersmith (ch. 13). I will review these three.

It's very easy for me to start out with my own. I will review it only briefly since you have the text (ch. 12). From 1930 through 1965 about 400 publications have appeared. I can narrow them down to 97 sources. Almost all included retinopathy with or without other complications, and comments on the effects of controlling diabetes on the rate of progression of vascular disease were made. Fifty-eight believed a positive relation existed. Twenty-nine thought there was insufficient evidence to support a relationship. Only 10 felt that the subject was too complex to come up with an opinion.

In going through the studies in detail I did not find any that satisfied me from the standpoint of experimental design (*1*). In particular, all centers except two used retrospective data. The authors went back and looked at charts that somebody had written something on 10 years ago. For example, in my hospital in 1948 I was a member of the house staff, and I certainly was unskilled in observing diabetic retinopathy. If I wrote something on the chart about the retina, and somebody looked at my note today, he'd say, "Oh, Harvey Knowles is interested in diabetes. This must have been diabetic retinopathy." This points out, at least in our area, the spuriousness of utilizing data put in a record by somebody 10 or 15 years ago.

I was indeed pleased to hear Dr. Kohner refer to Schlesinger (*2*) in Holland. He and Rabinowitch (*3*) in Montreal are the only two I am aware of who carried out prospective studies. They started at time zero with a certain number of patients and plotted what happened to the patients over ensuing years.

The measures of control are extremely difficult to establish. Dr. Lundbaek, in his book in 1953, wrote an excellent section on the problem of estimating the day-to-day control in the diabetic patient at

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home, when the patient is seen only several months in the clinic or in the office. Control means different things to different authors, and this has led to a whole host of measurements, none of which is efficient in itself.

I was listening to the discussion today of reading eye photographs. I know from studies I am involved in now that there can be an appreciable error of reproductibility not only between readers of photographs, but within readers as well. A reader of a certain eye photograph sees two small spots today and when he reads this picture a year later he may come up with a different answer.

I was very pleased to learn that Dr. Caird and Dr. Kohner have taken a stand opposite to mine in that they feel they have data supporting a beneficial effect from good control.

Dr. Caird, I hope you will correct any misinterpretations of your data which I present here. In 2,000 diabetic patients observed at the Radcliffe Infirmary from 1949 to 1965—that would be over a 16-year period—3,500 eye examinations were made. This amounts to about one and a half per patient. Of the 2,000 patients, 593 did not have retinopathy at first observation. This low figure of retinopathy would suggest that bias in selection for ophthalmological examination was present in that those referred were thought to have lesions. When the 593 were observed later, 235 had developed retinopathy. Now Dr. Caird separated the patients into those that did and those that did not develop retinopathy. He measured their glycosuric scores. I summarize his three points here as follows:

(1) That there was a positive relation between the presence of retinopathy and degree of glycosuria, at least in those under 60 years of age.

(2) That heavy glycosuria in the first years of known diabetes (in a group that had a mean duration of 4.8 years) was more closely related to the development of retinopathy than glycosuria later in the course of diabetes.

(3) That the degree of glycosuria had no effect on the course of the lesions once they were established.

I have followed Dr. Caird's work with great interest. But unfortunately it is retrospective in nature, unless he himself started in 1949 and plotted all the data each year from then on. Also, I do not know the reproducibility of measurements. But, I must say that many authorities would agree with his views.

Dr. Kohner, I am very pleased to see what was started in Hammersmith, because it is a prospective study. Dr. Kohner, your findings at 1 year from time zero are as follows:

There were 104 patients who entered the observation period with

retinopathy already present and in whom the rate of progression of retinopathy versus control of diabetes was measured. Control was estimated by blood sugars, urine sugars, and other traits such as gaining weight and frequency of hypoglycemia, if I interpret your paper correctly.

And I put on the board also, in chart form, the results of 1 year's observations, prospectively planned, of the relation of diabetic control to the progression of the retinopathy. Note that in the poor control group, the lesions progressed faster with a rate of high significance ($p<0.01$).

The method of grading the course of retinopathy is an excellent one. My only criticism of the work is the short time of observation. But I am pleased with the design, because we are desperately in need of prospective studies starting at time zero. With this approach a life table system can be developed to plot the cumulative risk rates and not just those of prevalance of events as they occur in the total diabetic population.

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Discussion of Relationship of Retinopathy to Metabolic Control

KNUD LUNDBAEK, M.D., *Moderator*

Dr. Lundbaek: As we all know, this problem has been discussed for a generation or more. It's perhaps no exaggeration to say that there is no field in diabetes where more nonsense has been heard and said than in this particular field.

We have seen tabulated here (when you go through all these papers) that 90 percent feel that the people who take care of their diabetes fare better. I think it should also be stated that nearly all of those who have stated this think the difference is a small difference. Now, 5 percent find no relationship. And 5 percent are philosophical about it.

Perhaps I'm wrong, but if there were no difference due to attempts at control, and 300 people have tried to look at it (most of them very badly of course), wouldn't you expect to find some papers who told you that good treatment made the eye much worse and gave you much more retinopathy? As far as I know, there is none. This doesn't prove the point but should be mentioned in connection with looking at old papers (which probably should not be looked at all).

The important thing, of course, is the prospective study. We have been discussing prospective studies and talking about prospective studies for so many years. As far as I know, however, there is only one prospective study going on in this country, by the university group diabetes program.

I was very surprised and very happy to see the results in London; namely, working with people who already have their retinopathy (ch. 13). Despite only 100 patients and a very short observation time, I'm not able to criticize them. I must say their paper is formulated and stated so I can see no fault in it. In this situation, by making a careful prospective study, it is possible to show that the general impression on which we all work is actually true.

Dr. Davis: In Dr. Kohner's and her colleagues' paper, aren't they comparing two different groups of patients? Aren't they comparing juvenile onset patients who, in general, are poorly controlled with

adult onset patients, many of whom are well controlled and are not taking insulin?

Granted that there is a significant difference between these two groups, is the difference due to the control or to the fact that these are two different groups of patients?

Dr. Kohner: It is easier to control some patients' diabetes than it it others. There is no question about this. But I don't think that the findings we have here are similar to those that were found by other people. In fact, Constam found that patients with mild diabetes, who could be treated by diet only or by diet and tablets, fared worse than the patients, or at least no better than the patients, who were insulin requiring (G. R. Constam, Zur Spatprognose des Diabetes Mellitus, Helv. Med. Acta 32: 287–306, November 1965).

Dr. Caird's findings are that the older you are when you start having diabetic retinopathy, the worse the prognosis. And, after all, the patients who are adult onset diabetics started diabetes a great deal later than the juvenile onset diabetics. So although we are dealing with two different sets of patients, I think that our findings are still valid.

There is a further point here, and I just touched on this in the discussion of our paper—that a great number of the patients who only reached "fair" control in our series had, in fact, a marked improvement in diabetic control over the previous diabetic control.

You very often can't reach "very good" control in late stages of diabetes when you have other complications. You can't reach "very good" control for simple reasons, such as a diabetic stomach which absorbs food irregularly. He gets 2 percent urine sugar one time and gets hypoglycemic episodes at others. Patients very often will vomit, and you find they come to the clinic for their blood sugar in a worse condition than normally. This is usually more marked in the patients who have longstanding diabetes with other diabetic complications. As it happens, they are mostly in "fair" and "poor" control in our group.

Dr. Lundbaek: Still, the important answer to your question is, of course, that the risk of developing severe vascular disease is the same in young and old diabetics, and this has also been shown by me.

Would you agree, now that you have already been lucky enough to get this result so easily, that it would be especially nice for you to do that same kind of study with young patients in one group and old patients in another? You probably would get the same results.

Dr. Kohner: I don't know where you get the idea this was an easy study.

Dr. Lundbaek: Well, it's only 1 year.

Dr. Kohner: 22.9 months.

Dr. Lundbaek: I mean as against 25 years.

Dr. Kohner: Well, I think the interesting point would be to start seeing patients much earlier, before they have retinopathy.

When I did my analysis, I didn't expect to get any positive results at all. And I was more astonished than anybody else when it turned out this way.

Dr. Knowles: Dr. Kohner, do you feel that blood sugars you get when patients come to see you in the clinic or in the hospital give you a true picture of the chemical control of your patients?

Dr. Kohner: I don't think that I can say exactly what a patient's diabetes is doing over 24 hours a day over 22.9 months. I think we get an estimate of diabetic control. I tried to establish their threshold. I tried to get the patient to test the urine at least two or three times a day. Some patients do so more often. I think this is as near to seeing what happens to a patient as one can reasonably get.

In some patients, where I had some doubts about whether the patient was testing his urine correctly or whether he was particularly good at keeping to his diet 24 hours before he came to the clinic, I did unexpectedly go to his house and did both urine and blood sugar on occasion. These, of course, were limited in number, and no patient had it more than twice.

Dr. Knowles: In my experience, the clinic sugars are different from what I call "unsuspecting sugars," which I collected at home and published some years ago. I had a nurse who got them when patients came out of school or were walking down the street. They didn't expect to have a blood sugar drawn. Or if they came to the hospital for an X-ray, not to see me, we were waiting to get a sugar. This is very different from the sugars on regular clinic visits. That's why I wrote some time ago about the problem of really estimating day-to-day control.

I'm sure, in your country, patients do very well at home. In our country, at least in my experience, many prepare themselves to visit us, and they know I am going to get a blood sugar. Finally, I got to the point I wouldn't tell them when I was going to get it. The juvenile diabetics I deal with weren't the same at home as they were when they came to the office.

Dr. Fraser: When Dr. Kohner started on this study, we all said there was no point in doing it unless she made an effort—which as far as I know is never made—to get an idea of what happens 365 days out of the year. Of course, she didn't achieve that. And I suppose it would be a fairer comment to interpret her data as showing that very bad control has an undesirable effect, rather than showing that good control has a desirable effect.

Dr. Oakley: Many of the juvenile onset patients were actively im-

proved, in terms of their treatment, by alteration of their type of insulin regimen. I think this is important. Many of these cases, who perhaps had poor control on a single injection of insulin a day, were subsequently put on a regimen that appears to give the maximum possible insulin action a maximum number of times a day. That is, twice-a-day injection of a mixture of short-acting and intermediate-acting insulins. This, in itself, achieves as good control as one can get in any one patient. We don't know any way of getting any better control. The juvenile group were all intensively treated in this way, and the achievement of even "good" or "fair" control did often represent appreciable improvement from the previous state of affairs.

Dr. Balodimos: I studied 150 patients at the Joslin Clinic who had "mild diabetes." They were taking no insulin at all, or, if they took insulin, it was under 30 units, or they were taking oral hypoglycemic agents for many years. I found a 40 percent incidence of retinopathy, and again there was effective control. The point I wanted to make is that mild maturity-onset diabetes frequently has retinopathy also.

Dr. Keen: There is controversy among the British as to whether we can't find a better term than "diabetic control." What we are looking at presumably is prevalent blood sugar. And this doesn't depend only on the control that is exerted over it. Maybe I can give you an example to clarify what I mean. Six years ago we carried out a survey of undiagnosed diabetes in a town in England, and we found about 400 previously undiscovered diabetics. We defined this as people who had blood sugars in excess of 120 milligrams percent 2 hours after a standard dose of glucose. When we divided these newly found diabetics into groups, those from 120 to 200 and those above 200 milligrams percent—that is to say, a lower and an upper group as far as their degree of diabetes was concerned—we found 2 percent of the lower group had retinopathy at the time of discovery; that is, typical diabetic retinopathy. And 13 percent of those with blood sugars over 200 milligrams percent had retinopathy at that time. In the numbers that we studied, this was a highly significant difference. And, of course, in this group all were diabetics. The question of control didn't come into this at all. They hadn't been known to be diabetic before, and there hadn't been an attempt to control them. They had been exposed to blood sugars at quite different levels for an unknown length of time. What one is looking at, when one looks at the blood sugar level they are running, is the prevailing blood sugar to which they are exposed. Control may well influence that, but it is only one of the factors which alters the level of blood sugar.

What we really want to know is, if we take a group of diabetics that are poorly controlled and control them half well, and leave the other

half as they were, are they going to be better off? Surely, what we need to do, if we are doing a prospective study, is treat half the patients in a special way and leave the other half treated in the ordinary way.

Dr. Kohner: When our study was first started, the idea was that all patients who were born on even days would have very strict diabetic control, and all the patients who were born on odd days would have their treatment unchanged, and nobody would do any alterations. It was also decided that I would see the patients who had the very strict control, and the rest of the diabetic clinic doctors would see the other patients. Within 3 months this had to be abandoned, and there were various reasons for abandoning it. One was that doctors in the clinic felt that, as I way trying to get very good control in some patients, they couldn't possibly do worse. So everybody suddenly started to change their patients' treatments.

Also, these patients were picked up because there was a diabetic survey done, and these patients were found to have retinopathy on that survey. Now, many doctors felt that once they found diabetic retinopathy in a patient, unless the control was already good, they really had to try and improve it.

The third reason it fell down was that there were a number of patients who did have diabetic retinopathy and had intercurrent illness like tuberculosis or something, and it was felt that you had to get the best control for treatment of the intercurrent illness.

Dr. Joplin: We have been discussing the comparison of different levels of control throughout a period of time. There are also some results from imposing good control on patients who hitherto had poor control as against those who had pituitary ablation. In this formal control series there are a small number of patients in whom imposition of very much better control over a period of a few months resulted in as spectacular an improvement in both new vessels and hemorrhage formation as we have ever seen after pituitary destruction. Admittedly, this is a small group of patients, but the fact is it can happen.

Dr. Caird: I would like to comment on Dr. Kohner's last remarks. They show excellently, of course, the fact that prospective trials have their difficulties too. If I might present some data to show what happens not when control is deliberately imposed but when the glycosuria percentage (in my terminology) changes. These data are from the study of 299 patients for the period of 10 to 14 years between diagnosis and the index eye observation, divided into two halves, the first period of about 5 years and the second period of the remainder (table I).

There is a large number of patients in whom the glycosuria percentage was under 20 in both the first and second periods. Thirty-eight percent of them had retinopathy 10 to 14 years after diagnosis.

TABLE I.—*Frequency of retinopathy in relation to variation of control of diabetes (Caird, Pirie, and Ramsell, 1968)* [1]

Glycosuria percentage in—				
1st period	≤19	≤19	≥20	≥20
2d period	≤19	≥20	≤19	≥20
Proportion with retinopathy	47/123	14/38	24/44	57/94
Percentage with retinopathy	38	37	55	60

[1] Caird, F. I., Pirie, A., and Ramsell, T. G.: *Diabetes and the Eye.* Philadelphia, F. A. Davis Co., 1968.

Now, if the glycosuria percentage in the first period was less than 20 but in the second was over 20 there is a small number of patients whose frequency of retinopathy is effectively the same (37 percent) at the end of the second period. When we take the other pair, a glycosuria percentage of more than 20 percent followed by more than 20 percent, then the frequency of retinopathy in 94 patients was 60 percent. When we take ones who, for one reason or another, had a glycosuria percentage more than 20 percent in the first period and less in the second, we find effectively no difference; 55 percent had retinopathy.

My conclusion from this is that it is the first period that matters. If you change the control later on, it is still what happened in the early years that matters.

Dr. Bradley: As a member of a clinic well known for efforts to control diabetes, I have been harangued for 20 years by all kinds of people about how ridiculous our ideas were, I now realize I don't have to say very much tonight, and I'm delighted. I'm delighted with Dr. Kohner's paper, and I just hope that she or someone will continue this work. I recognize the problems in a prospective type of study. When you try to control a certain way, it's either that the patient doesn't cooperate or the other doctors in your clinic don't cooperate. But it still is worthwhile to continue it. And if the numbers are large enough over a period of time, I think it will be very worthwhile. I think one of the reasons why it has been so difficult to evaluate this problem is the inexorable tendency for microangiopathy in diabetes to progress with time. If you follow a young diabetic patient who has no other real factors involved long enough, almost all of them eventually will begin to show microangiopathy. If you do studies early in the course of the disease, you can show morphologic changes. As you well know, in the group of juveniles that Dr. White reported some time ago, after 20 to 40 years of diabetes, something like 93 or 95 percent had retinopathy. This simply means that if you follow them a little bit longer, I am sure that 100 percent will have retinopathy.

Now, if you combine that with the observations which many of us have made over the years and you ask people these questions, "Well, what about the patient who has frequent bouts of coma and gross

insulin deficit over the years? How do they fare?", most people seem to agree that they will develop microangiopathy of a significant clinical degree more rapidly and will get into trouble much earlier. Some people have elected to extrapolate this sort of observation into controlling diabetes better. Somewhere between these two observations lies what I think is the most important point here; that is, that in order to control diabetes well enough to give people real protection is extremely difficult in the great majority of cases. It's very hard on the patient, and it's hard on the doctor. Even though we still would feel that controlling diabetes is extremely important, I think this is only one of the steps. We must do something more. It is a tremendously difficult task to expect young people with diabetes to control the diabetes well enough. Those patients who do well are often described by others as being undesirable people, because they are compulsive. And we can pinpoint this group of compulsive people who always take extra insulin three or four times a day, every time they show sugar. Yet those are the people one can cite who have diabetes 30 or 40 years, and clinically you find little or no evidence of microangiopathy.

Even though we might arrive at some conclusion regarding control, we still have the problem to do something more than just controlling diabetes.

Dr. Lundbaek: Perhaps somebody in the panel would like to answer this question.[1] It is headed "Controversy." "Dr. Caird said one cannot affect progression or regression of background retinopathy once it is started. Dr. Kohner et al. disagree. Why?" Why don't you, the two of you, explain to us how it's possible?

From Dr. Caird's paper, I got the impression that if you just treat your diabetic patients well the first 5 years, then you don't have to treat them any more. From Dr. Kohner's paper, I got the impression this is not right.

Now, tell us the truth, please.

Dr. Kohner: I think there are a number of differences between the two studies. The observations made in Dr. Caird's studies were done by a great number of different ophthalmologists and at a great number of different times. It's a retrospective study relying entirely on description. We have already said that description has its disadvantages, and different observers have their disadvantages. There is always an observer error. We try to minimize this, and we have photographs of all these patients. And although I did a study of all of them, the photographs are available for anybody to check. We keep them. I think this is one of the differences. The other difference

[1] EDITORS' NOTE.—Certain written questions from the floor were relayed to the panel by the moderator.

is that I think our definition of diabetic control is very different. Also, our study is a shorter one, and maybe if we study our patients for 15 years, we will come to the same conclusion as Dr. Caird.

Dr. Lundbaek: Your patients will not live for 15 years.

Dr. Kohner: I hope some of them will.

Dr. Lundbaek: Very few.

Dr. Caird: I'm sure that the difference really resides in the degree of sophistication of the methods of study. In my study they were very unsophisticated indeed. What I was trying to say it, good control matters less and less as you go along. I wouldn't want to be saying that it never matters at all.

Dr. Lundbaek: Well, I suppose this is the nicest kind of agreement we can get from the two of you.

Dr. Fraser: Dr. Caird has pointed out they are not necessarily in disagreement at all, that what Caird has shown in the relative importance of the early and late years could well be true of Dr. Kohner's study. There is no contradictory evidence.

A general point we should all remember here, too, is that statistics can only show a difference. They can never show that things are the same. And this is a very important point to remember.

Dr. Lundbaek: Still, it's odd they found the difference in the beginning and not in the end where you found it.

Dr. Fraser: Any difference is important. Any similarity is irrelevant.

Dr. Lundbaek: Absolutely.

Dr. Norton: At the risk of displaying my ignorance, I would like to have explained to me if some x factor (that makes control of diabetes difficult and also contributes to retinopathy) has been excluded. There seems to be an emphasis on control and sugar level. It seems to me that you could have another factor which manifested itself in both parameters.

Dr. Knowles: I hope I didn't get the idea across that I firmly believe that if we control them best we would have less vascular disease. My whole crusade has been trying to find evidence for that hypothesis. I have never really said that control had no effect at any time. If I did, I would be making a type II error of experimental design. Just because I don't have evidence for something doesn't mean that that thing doesn't occur.

But to answer your question, the point is that no matter whether the patients come from Bradley, who really works with them, or me, who has the worst control of diabetes in the world, or somebody else in the audience, they all get vascular disease sooner or later. And if control

plays a role, either its influence is small or else we aren't really able to apply it, as Dr. Bradley suggested.

I think that the underlying factors here which you asked for, the *x* factor or genetics, are really something much deeper than anything we are measuring today.

Dr. Caird: I'd like to make one comment on genetics. I have an as yet unpublished study of 75 families in which more than one member participated in the investigation that I have mentioned. And we found no evidence at all of families who got retinopathy more than others. I think the suggestion of geneticaly influenced retinopathy is totally without any evidence whatever.

Dr. Knowles: I'm very disappointed.

Dr. Caird: The data I have presented, where a third of the patients apparently changed halfway along the line and turned from good diabetics to bad ones and vice versa, suggests it is what the doctors do, rather than the fundamental nature of the diabetes that matters.

Dr. Bradley: Regarding Dr. Caird's comment about not being able to improve retinopathy with improved control once it is developed, if one were again to turn your coin around and take a patient with long standing diabetes, 10, 15, or 20 years or more, who has some retinopathy, and let him be exposed to a state of grossly uncontrolled diabetes, like diabetic ketoacidosis, our experience has been that this literally lights the fire as far as progression of the disease is concerned.

Dr. Lundbaek: This is your clinical impression?

Dr. Bradley: Yes.

Dr. Lundbaek: You have not studied that?

Dr. Bradley: Not in any statistical way.

Dr. Lundbaek: What we have been discussing is only what all of us have believed before. Now, with two papers like this, perhaps some of us have come to think that we know that low blood sugar is correlated to less damage of the vessels.

Now, how you produce a lower blood sugar and the fact that there are some patients in whom you can do it and some in whom you cannot do it (because there is something wrong with you or with the patient or with the *x* factor or something) are other questions which are not answered.

I think it is very important to get evidence to support even more firmly that there is a relationship between the blood sugar and the occurrence of vascular disease.

I would like to ask Dr. Kohner why she included information about fat loads and frequent hypoglycemias. If you classify only on sugar in blood and sugar in urine, do you get the same results? This is easy to answer either yes or no.

Dr. Kohner: I get the same results.

Dr. Roth: I would like to direct a question to Dr. Field. Does he feel there is any significant difference in the posthypophysectomy patients between those with good diabetic control and those who have instances of poor control following surgery?

Dr. Field: I agree with Dr. Bradley that if this control (however we achieve it clinically) is significant, it must be a weakly determinative factor. The exceptions excite me more than the rule. We see patients with violent neovascular retinopathy who are discovered to be diabetic because the ophthalmologists found the retinopathy, but who don't spill any sugar and who have very modest elevations of blood sugar; for example 140 to 150 milligrams percent. We hypophysectomize some patients who have had large insulin requirements and have had intensive glycosuria despite our intensive clinical efforts (albeit not as good as in London), and find the spillage is the same after surgery as before. Yet, they will have what we term a brilliant result.

So I am confused by the whole matter.

I am, however, prepared to believe that negligence and repeated episodes of ketoacidosis don't make good sense and are, perhaps, a factor in bringing about an early expression. If Dr. Caird's paper is correct, if it is the early phase of the matter that appears to be the period of determination, this excites me to some extent in believing that perhaps this is an induction of an immunization, an inception of a phase which thereafter becomes a self-propagating vasculopathy which is divorced from its original, causative factor.

Dr. Kohner: There could be another point here. The first 5 years of a patient's diabetic life is the time when the patient will get into a habit of keeping to a diet, of doing all sorts of things fairly regularly. After all, this is most important in diabetes, especially if they eat much the same each day and if they get much the same amount of exercise each day. If you have good control in the first 5 years, all this means is that you have achieved a habit in the patient to do this. Possibly the habit stays with the patient, at least to some extent. That is why the first 5 years may be so important. Maybe the patient just doesn't test the urine after the first 5 years.

Dr. Lundbaek: That is why I personally disagreed with Dr. Caird's paper where he says:

> One interesting consequence of this view is that it will prove difficult or impossible to show any relationships in control and retinopathy ——— in which a considerable portion of patients were entered after having diabetes for some years.

Most people have found such a relationship.

Dr. Caird: I was thinking particularly of Dr. Knowles' study where he found no difference. And as far as I was able to determine,

about half the patients had had diabetes for 5 years when they were entered into the study, and they would be therefore diluting the patients in whom a relationship could be demonstrated.

Dr. Oakley: I would like to make two points. Firstly, when we are talking about control, we have got to know exactly where to set our lines of demarcation. In the early days of studying diabetic pregnancy, in looking at what we thought were good and bad control, we considered the effect on the fetus. When you achieve good control, it seems to have a good effect. In the case of retinopathy and vascular complications, we have a long-term experiment, and it is going to be much more difficult to achieve the degree of control we like to get in our pregnant patients over a period of 20-odd years. So it's impossible to say that the whole answer doesn't lie in control. It could. But it is almost impossible (and may be impossible) to achieve the degree of control we get in pregnancy.

The second question appears to be the method by which the control is achieved. Should we, in fact, put our patients with retinopathy on insulin rather than put them on tablets? Should we put our patients who are on long-acting insulins onto multiple injections of regular insulin, or soluble insulin as we call it in England? It is very difficult to accumulate data in this respect, but maybe the method of treatment is more important than the degree of control achieved, or perhaps the degree of control achieved does really relate to the method. But the methods that we have of assessing control don't themselves relate to the actual degree of control achieved.

Dr. Lundbaek: I have one written question to Dr. Caird. It is very simple to answer. "Is severity, not frequency, of retinopathy influenced by control?"

Dr. Caird: I had not really wanted to discuss this, because it involves the statistics of very small proportions (table 2).

Here we have the proportion of patients in the 299 with 10 to 14 years of diabetes who have proliferative retinopathy 10 to 14 years after diagnosis. They are divided into two groups, those with a glycosuria percentage of over 40 and those with a percentage under 40. The distinction is in fact, between very bad control and the rest.

TABLE 2.—*Proportion of patients with proliferative retinopathy 10 to 14 years after diagnosis of diabetes*

	≤39	≥40	Significance of difference
Glycosuria percentage in—			
Whole period	3/233 (1%)	7/66 (11%)	0.001
1st period	2/219 (1%)	8/80 (10%)	0.001
2d period	7/242 (3%)	3/57 (6%)	NS

The very badly controlled patients have a frequency of proliferative retinopathy of 11 percent, but there were only three patients in over 200 in the better controlled group with proliferative retinopathy, giving a frequency of 1 percent. This difference, within the limitations of statistics of that sort of proportion, is very highly significant.

When we do this again for the first and the second periods, we get the same answers as before. The difference is highly significant in relation to the first period, and there is no significant difference in relation to the second period. Thus, with all the limits that are imposed on this particular type of study, the severity of retinopathy is correlated with the glycosuria percentage.

Dr. Knowles: Was this based on the chi square test of multiple attributes?

Dr. Caird: No. This was based on Fisher's exact test.

Dr. Lundbaek: In experimental diabetes in the rat, is it of any interest that kidney changes are histologically and histochemically and electron microscopically very, very close to what you get in human beings? And is it of any interest that you also get changes in the eyes in these animals? Are there any comments on the question of drawing inference from animal experiments? It is a perfect model, except that a rat is not a human being. I personally think there is very little difference. Besides that, it's a perfect model of insulin deficiency.

Dr. Caird: It seems to me that the demonstration of these lesions in four species of animals makes the hypothesis that angiopathy is a built-in part of idiopathic human diabetes totally untenable. The hypothesis requires that both the genes for human diabetes and human diabetic angiopathy are in any rat you happen to pick up in the street.

Dr. Lundbaek: As far as the rat goes, we know the common white rat is rather resistant to diabetes. They don't run around in the gutters with it in their genes.

Dr. Packman: Many of us see very brittle, juvenile diabetics, and all we can do is keep them free from ketosis the best we can; keep their blood sugars relatively normal; and keep them from hypoglycemic reactions. Within these limitations, is fine adjustment of diabetes really necessary?

Dr. Kohner: It just depends what you want to achieve. If you have already got angiopathy, all you want to achieve is the slowest possible progress of that angiopathy. The data I have indicate that you should try to get the most control you can get in that particular patient, and you probably can improve on it.

Dr. Bradley: I would agree with what Dr. Kohner says. One should try to control the brittle diabetic as well as he can for that individual. Our particular objective is to try to have him reasonably

sugar free both before breakfast and again at supper—two points in the day. Now, what is the precept for this? Only that this is about the best you can do. If you do that well, I think you are doing awfully well in the brittle patient. You may have to accept intervening bouts of hyperglycemia. This may be a rather naive way of looking at it, but, in our trying to think about control in patients, we have seen those who have had diabetes of this type for 30 or 40 years and still have little or no microangiopathy. You may say this is their inherent vascular system. But very often there are intelligent people who, despite being brittle, have managed to be reasonably sugar free at least twice a day over the years. Perhaps during that period of time they put something back in order metabolically. I don't know. And perhaps this gives them some degree of protection.

Dr. Lundbaek: Everything we have been discussing has nothing to do with the doctor's approach. We have been discussing strictly a question in natural sciences. Is there or is there not a relationship between blood sugar and the development of vascular disease? Now, it so happens that many of us who are here tonight, besides being interested and more or less involved in natural sciences, are also doctors. Faced with this particular patient at this particular time of his life, we have to discuss with him and explain to him as well as we can today's situation. This situation is a little bit different than it was yesterday. A patient might tell you quite openly that he will prefer not to be treated. That's all right. In this question we are just back to the way that a doctor faces a patient and weighs with the patient the pros and cons for doing this or that. But we need to have this natural sciences question answered in order to know what to tell the patient and to give him our best possible advice.

PART IV

Pituitary Ablation

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CHAPTER 15

Pituitary Ablation and Diabetic Retinopathy in Perspective: An Historical Summary

RICHARD A. FIELD, M.D.

One may rightfully ask why we should take the time to make an historical survey of this subject, and I was surprised when the editors requested me to do so. But, having made it, I think it has knit together my own perspective of the problem. Billroth was quite correct when he said:

> Only the man who is familiar with the art and science of the past is competent to aid in its progress into the future.

So, let me take you on a quick trip through history in regard to diabetic retinopathy and the use of pituitary ablation in its treatment.

It is altogether fitting that this variegated group meet together; that is, ophthalmologists, neurosurgeons, and internists. The whole history of the science of endocrinology in regard to the pituitary and of attempts to operate on the pituitary and manipulate its function comes primarily from the anatomic situation of the pituitary in physical relationship to the optic nerves. It has been the ophthalmologists, seeing their patients go blind, who have given the spur to neurosurgeons to get busy and help out and preserve vision. This goes back to the very beginning. It has been the endocrinologists who have been bringing up the rear in this field.

Most of the information concerning the physiology and pathology of the pituitary has come from the empiricisms established by neurosurgical procedures in attempts to remove tumors. An amazing fact is the amount of confusion which existed as to the various functions of the pituitary and how long it persisted without being set aright. We need have little fear that the frustration and confusion we feel about the subject under consideration today is without precedent.

Actually, recognition of diabetic retinopathy is a relatively recent event. Diabetes itself was thought to be an exceedingly rare disease until Sydenham. It was not until the chemistry of sugars became known and the ability to determine the blood glucose became a reality that it became possible to appreciate the widespread occurrence of diabetes.

In 1856, 118 years ago, Yaeger first described the occurrence of specific retinal changes in diabetics. In 1890 Kirschberg gave a systematic description of the changes of diabetic retinopathy. However, that did not satisfy everyone. Articless appeared *pro* and *con* for some 20 years afterwards as to whether there really was a specific type of retinal change in diabetes or whether it was merely a problem of atherosclerosis, hypertension, or renal disease.

Let us leave diabetic retinopathy for a moment and go to the pituitary. In 1886 Marie described acromegaly, and he put an end to an idea that had been handed down from antiquity that the role of the pituitary was to secrete mucus into the nose, although some people who have been involved in various transsphenoidal techniques begin to wonder whether it maybe is to secrete spinal fluid into the nose.

In any event, in 1887 Minkoswski, of the pancreas-diabetes relationship fame, related acromegaly to a disease of the pituitary gland. For 20 years afterward, the notion persisted that acromegaly was the result of pituitary insufficiency. It was not until successful surgical approaches to the pituitary, both in animals and man, were possible that this confusion was clarified. In 1889 Horsley was able to hypophysectomize dogs and have them survive. In 1909, Harvey Cushing, by hypophysectomy experiments, definitively demonstrated that hypofunction was not the cause of acromegaly, and suggested that hyperfunction was. In 1912 the classic Cushing monograph was published and became the factual basis of the knowledge of hypopituitarism and hyperpituitarism, and gave the stimulus to physiologists and concerned chemists to investigate the functions of the pituitary gland. In 1922 Evans and Long produced the syndrome of giantism with extracts of pituitary. In 1925 Bailey and Davidoff showed the histology in acromegaly was that of an acidophilic adenoma.

It is reported that Horsley did intracranial operations on humans as early as 1889. He started by approaching the pituitary from the frontal route but later went to the temporal route.

Throughout the course of this brief history, we see oscillation back and forth. What was the initial methodology was abandoned, and only later was reinvestigated and became the ultimate method of choice. The difficulties with the temporal route proved considerable, and, at that point, many felt that any operation at the base of the brain was unethical and immoral. Marie himself so stated. In 1906 Schloffer, mindful of the anatomy and some previous work that had been published, began the attempts of reaching the pituitary transsphenoidally using a supranasal approach. In 1909 through 1911, Oscar Hirsch and Harvey Cushing modified the transsphenoidal route and adopted an intranasal submucous approach. At about that

same time, radiation was becoming a very useful tool, and most surgeons who did operations on pituitary tumors followed up their surgery with irradiation.

In a report by Gromygda, the actual correction or improvement of acromegaly was attributed to radiation alone. In 1912, primarily through the work of Charles Frazier in Philadelphia, there was a return to the intracranial type of operation. In 1922 the second case of irradiation of pituitary tumor with good success was reported in the literature.

In the 1930's the work of Houssay related pituitary function to diabetes with the demonstration of the "Houssay phenomenon" or the amelioration of pancreatectomy diabetes by hypophysectomy. In rapid fire order thereafter, many physiologists and endocrinologists were able to show that diabetes responded to manipulation of pituitary activity in a more dramatic and sensitive fashion than to any other endocrine alteration one could make in the animal.

I am told, but have not been able to find the reference, that, in 1936 a French surgeon performed a hypophysectomy specifically for diabetic retinopathy.

However, the stimulus for the whole field of therapeutic hypophysectomy for diabetic retinopathy began in 1952 with Luft and Olivecrona, who were also interested in the effects of hypophysectomy on inoperable metastatic cancer. They also turned their attention to its effect in diabetes. Until yesterday, I had labored under the belief that it was the striking observation of Poulsen in describing the regression of retinopathy in his patient with Sheehan's syndrome that had provoked Luft and Olivecrona to explore hypophysectomy in diabetes. However, I stand corrected through the good offices of Dr. Lundbaek, and it seems there was a simultaneous development with Luft and Olivecrona actually undertaking their attempts before the description by Poulsen.[1]

In 1953, practically simultaneously, Talairach and Fraser began implantation through a transsphenoidal route of radiation sources, both radio-gold and yttrium-90. In 1955 Pearson and Ray reported on the effects of hypophysectomy in diabetic retinopathy. Later, Gordon and Javid published six or seven cases. At about the same time, George Ehni in Texas published his experience with a handful of cases of hypophyseal stalk section.

In 1958 John Lawrence at Berkeley began the application of heavy particle radiation toward producing hypopituitarism in diabetic patients. In 1961, after 2 or 3 years of experience, Dr. Sweet, myself, and several colleagues, including Dr. Charles Schepens and Dr. Joel

[1] EDITORS' NOTE: See Chapter 25.

Contreras, published a paper about stalk-sectioned patients. I think our contribution in this matter rested on the precision of the ophthalmologist in documenting the changes that took place after a pituitary ablation and, secondly, on the rigid criteria for selection of patients. Thereafter, there has been a considerable proliferation of interest, both in employing surgery and in various types of radiation. I do not mean to offend anyone in the audience by leaving his name out of this roll call. It is my ignorance rather than a lack of importance of your work.

In the most recent past, we have had further technical advances which have come about through the modifications of stereotaxis, originally started for cortical surgery by Horsley, and developed for the transsphenoidal route by Talairach. Two of his students who worked with him in 1960 when they were young and both of whom are present today, Dr. Nicholas Zervas and Dr. Robert Rand, have extended the technique by employment of thermal changes as the destructive mechanism. Dr. Rand chose a cold approach and Dr. Zervas elected a hot one. These techniques have been brought to a state of high perfection and high safety. Also, we should remember that much of the capability in this field has resulted from the availability of inexpensive, easily available, substitutive hormones, and that antibiosis and other medical advances have vastly increased the capability of operation or manipulation in or about the pituitary fossa.

At this point in time, I believe there is a general, though qualified, acceptance that pituitary ablation does do something beneficial in regard to the course of retinopathy. Unquestionably, it does bring about a series of objective ophthalmologic effects. The group which has been slow in this tridisciplinary attack are the internists. Admittedly, we are dealing with patients near the end stage of a widespread, microvascular disease at the point where we presently apply pituitary ablation. The internists are delinquent, because they cannot provide either a biochemical, physiological or hemodynamic explanation for the pathogenesis of diabetic vascular disease, and they have not as yet been able to interpret what happens following pituitary ablation into a testable theory of mechanism. Such information would give us significant therapeutic advantage and allow us to intervene early in the retinopathic process at a point where effects would be lasting, *preventive*, and would allow the patient a longer and more productive lifetime with useful vision.

As I view the situation, the ophthalmologists have done a good job; the neurosurgeons have done a spectacular job. It is now up to the biochemists, physiologists, and internists to apply themselves and

their techniques of investigation so that the mechanisms involved can be accurately defined; not only as regards the influence of pituitary ablation, but also as regards the pathogenesis of retinopathy itself.

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CHAPTER 16

Fluorescein Photography in Proliferative Diabetic Retinopathy Treated by Pituitary Ablation

MARIOS C. BALODIMOS, M.D.
SEARLE B. REES, M.D.
LLOYD M. AIELLO, M.D.
ROBERT F. BRADLEY, M.D.
ALEXANDER MARBLE, M.D.

Diabetic retinopathy is among the major indications for fluorescein photography. Several publications have exhaustively discussed the subject (*1–12*) and many others have touched on it (*13–20*). This report presents our experience with fluorescein in the study of diabetics before and after pituitary ablation. Only two abstracts deal specifically with this subject (*21, 22*).

CLINICAL MATERIAL AND METHODS

Sixty patients with proliferative diabetic retinopathy who had surgical hypophysectomy or proton beam pituitary irradiation were studied at least once with fluorescein angiography of the retina. Several of the patients were followed with fluorescein photography before and at various intervals after pituitary ablation to follow the progression or regression of the eye changes (table 1).

TABLE 1.—*Fluorescein photography in patients treated with pituitary ablation*

Procedure for ablation	Number of patients	Fluorescein results				No follow-up after ablation	Fluorescein photography cannot be evaluated
		Arrest of angiopathy	Period after ablation (months)	Active angiopathy	Period after ablation (months)		
Surgical	38	19	31	12	14	6	1
Proton beam	19	4	38	6	20	5	4
Surgery and irradiation	3	1	20	1	24		1
Total	60	24		19		11	6

From the Elliott P. Joslin Research Laboratory, Department of Medicine, Harvard Medical School, the New England Deaconess Hospital, the Joslin Clinic, and the Diabetes Foundation, Inc., Boston, Mass.

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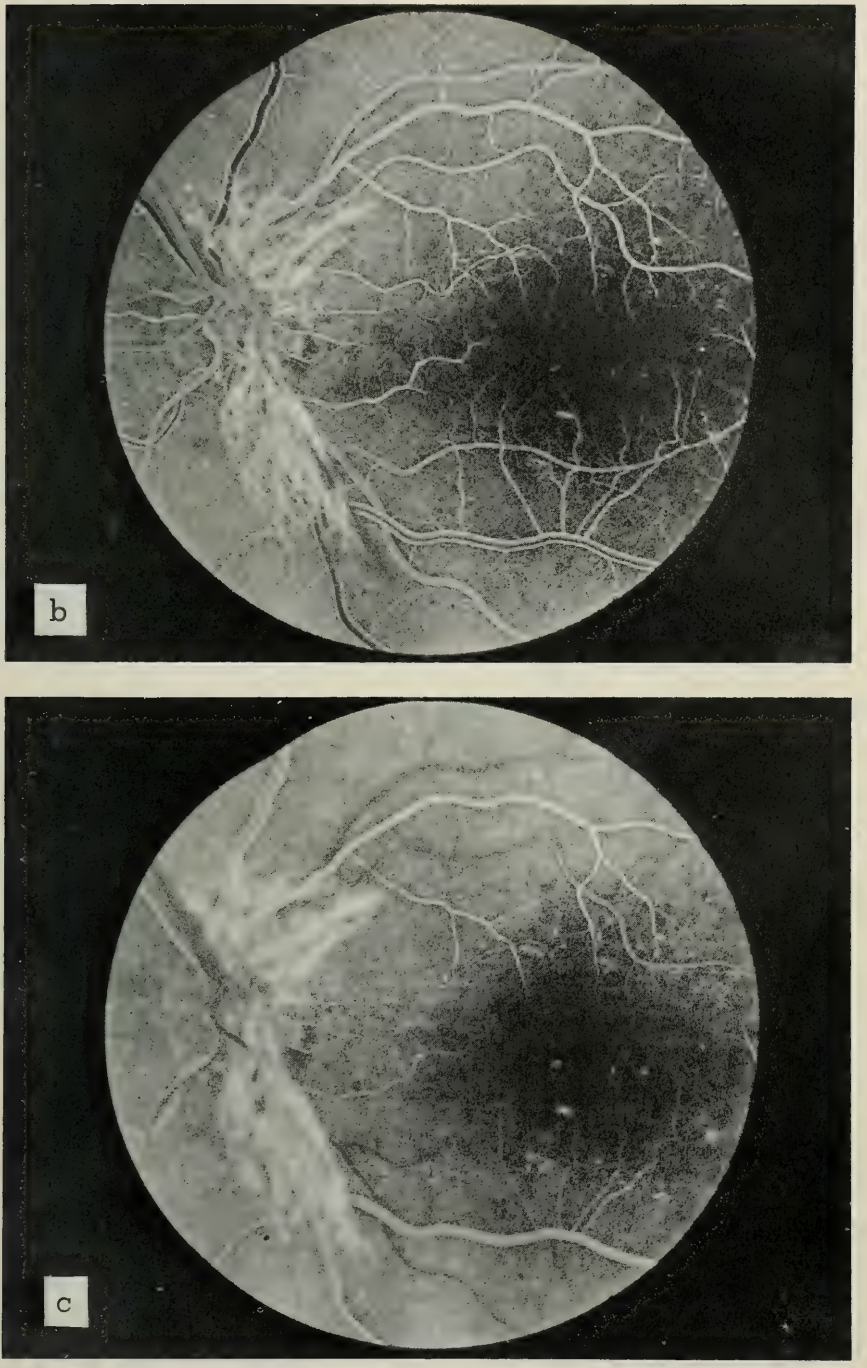
Ten milliliters of a 5 percent fluorescein dye is injected through an intravenous catheter within 1 second by using a Cordis injector. Serial photographs are take 1 to 3 seconds apart for the next 20 to 30 seconds.

A Zeiss fundus camera and a Nikon 35-millimeter camera with automatic film transport and a rapidly recycling unit for strobe light are used. Kodak Tri-X film has given satisfactory photographs.

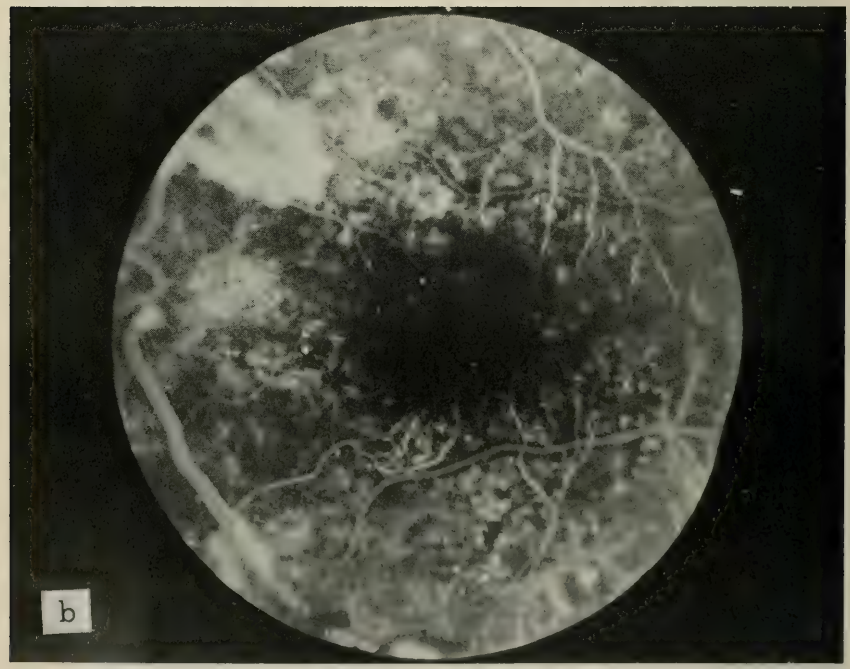
RESULTS

Diabetic Proliferative Retinopathy

New vessels arising from the disc (fig. 1a–c) or those forming the rete mirabile (fig. 2a–b) fill within a short time after the appearance of dye in the retinal arterioles. Two to four seconds later there is diffusion of fluorescein ("leakage") through these vessels, obliterating adequate view of the underlying retina and covering it with a patch of fluorescence. The extent of "leakage" does not necessarily correspond to the extent of new vessel formation as seen with the ophthalmoscope; depending on the activity of the angiopathy, even apparently small areas of new vessel formation may show pronounced permeability.



FIGURES 1 a–c.—*New vessels from the disc (a), show rapid diffusion of fluorcein (b–c).*



FIGURES 2 a–b.—*Rete mirabile is delineated with fluorescein (a) and becomes rapidly obscured by a patch of fluorescence (b).*

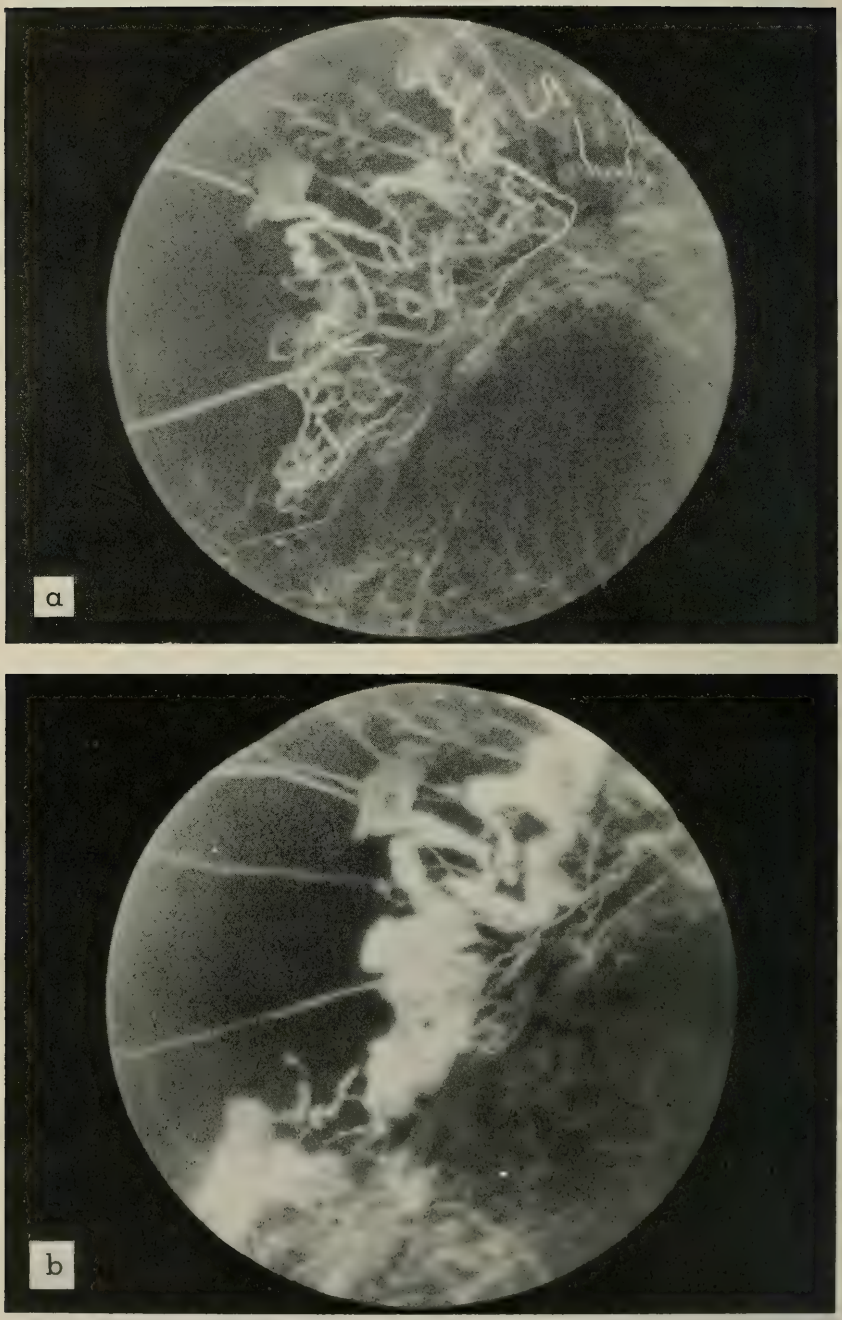
Bands of fibrous tissue with its accompanying increased vascularity behave similarly (fig. 3a–b). Seconds after entry of the dye a diffuse fluorescence extends to the borders of the connective tissue. At this stage the fibrous tissue represents new vessel formation with supporting matrix.

Frequently in cases of early neovascularization one or a few delicate new vessels and the supporting thin matrix are visible ophthalmoscopically, but there is uncertainty as to their pathologic significance. After fluorescein, diffusion of the dye from the suspected vessels will confirm the ophthalmologist's suspicion as to their nature.

Besides the demonstration of new vessel formation and in particular the activity of angiopathy the value of fluorescein angiography lies also in the demonstration of areas of avascularity ("capillary closure"). These are dark, irregular areas, surrounded by abnormal vessels in the periphery and multiple microaneurysms (fig. 4a–c). In active proliferative retinopathy irregular tortuous and distended venules are found. Characteristically some segments of either arterioles or venules retain the fluorescent dye after other parts of the retina, including the normal parts of the same vessel, no longer contain detectable dye (fig. 4a–c). It is suspected that the vascular wall of these abnormal segments has undergone changes resulting in the adherence or binding of fluorescein to it.

Some patients show a typical appearance on fluorescein angiography which we have called "diffuse angiopathy" (figs. 2b, 4a–c, 5a, 6a, 7a). The photographs show an increased vascularity, more capillaries being visible than normally. Many dots of fluorescein are observed around the macula and elsewhere in the posterior fundus. These represent presumably aneurysmal dilatations of capillaries (true microaneurysms). They appear confluent, hanging in clusters from the vessels, and should be differentiated from drusen (fig. 8) (*3*, *5*). These microaneurysms frequently surround soft exudates or areas of neovascularization or avascularity ("capillary closure"). Both these numerous new capillaries and the microaneurysms retain fluorescence longer than normal vessels and show a discrete diffusion of fluorescein into the tissues with blurring of the detail (figs. 4a, 5a, 6a, 7a). These patients may or may not have definite new vessel formation in some areas of the retina.

Large or small punctate hemorrhages (thrombosed microaneurysms or "red dots") and hard, waxy exudates themselves do not show fluorescence and appear as dark areas in the photographs. Simultaneous study of color photographs without fluorescein helps in their recognition, and differentiation from avascular areas of "capillary closure."



FIGURES 3 a–b.—*Highly vascular connective tissue (a), shows rapid diffusion of dye (b).*

After Therapy

Even in the first 2 to 3 weeks after a successful surgical pituitary ablation, the results of this therapy on the retinopathy become apparent. The major criterion of decreased activity of the abnormal process and of early improvement is a demonstrable decrease in the "leakage" from the new vessels. In general, the degree of diffusion (permeability) of the fluorescein can be correlated with the activity and severity of the retinopathy. In the early weeks the new vessels appear still patent and can be demonstrated, but the "leakage" decreases and with continued improvement stops altogether. (fig. 4a–c). A few weeks or months later the new vessels either obliterate or involute and are no longer visualized with fluorescein (figs. 4a–d/5a–b).

Bands of fibrous tissue continue to show fluorescein diffusion for a longer period, indicating persistent or continuing vascular activity. Only when the process has become definitely quiescent and the connective tissue transformed into a relatively avascular white scar does the "leakage" of fluorescein from its vessels stop. The fibrous band then appears white prior to the injection of fluorescein, showing no increase in its "glow" after the passage of fluorescein (fig. 9).

Neovascularization at the retinal surface, the dilated and tortuous capillaries and venules, and the "diffuse angiopathy" show a remarkable reversal toward normal after pituitary ablation (figs. 4a–d, 5a–b, 10a–b). The abnormal segments of vessel walls, and the areas of "capillary closure," represent anatomic alterations and are not expected to change as a result of pituitary ablation (fig. 4a–d).

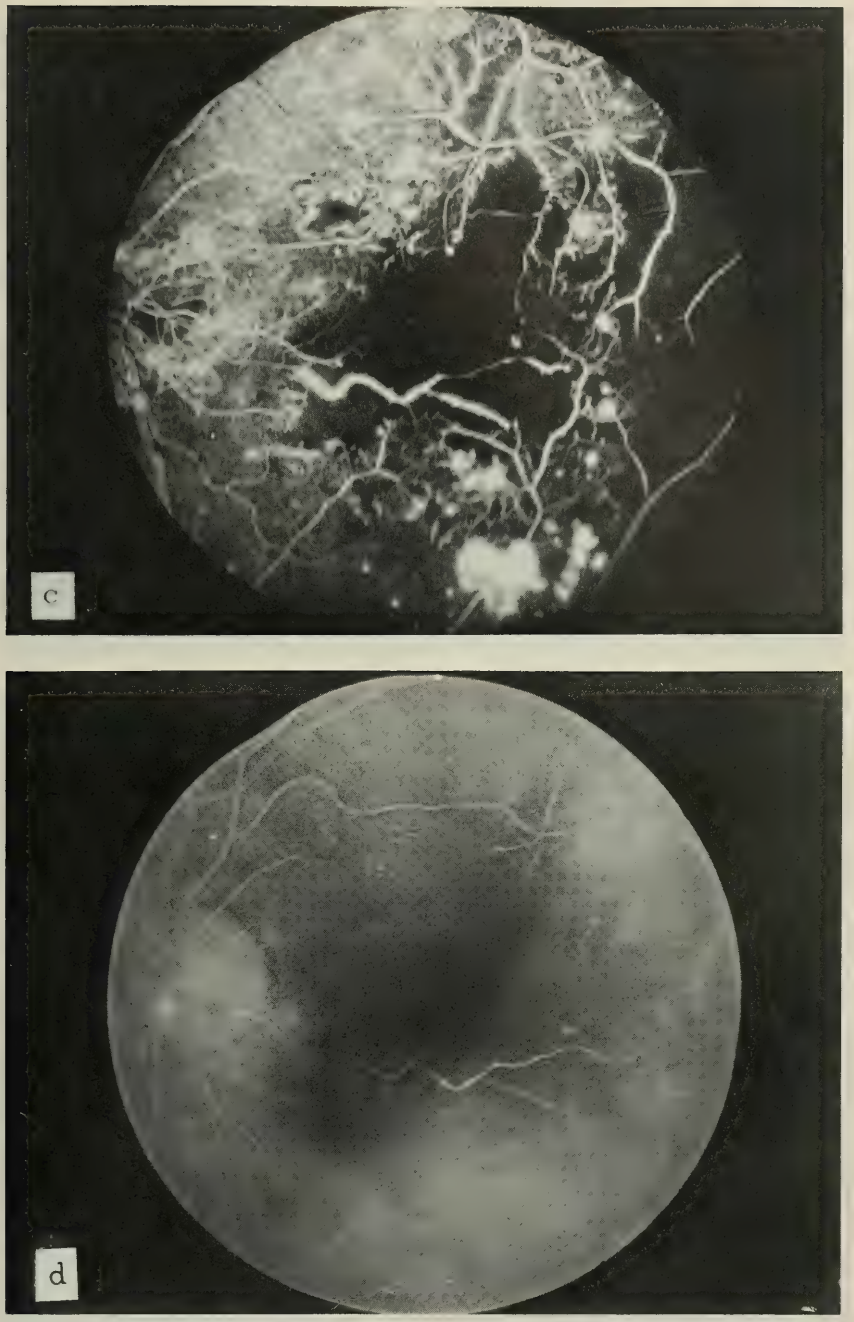
Improvement in the ophthalmoscopic and fluorescein findings in patients with incomplete pituitary ablation is only partial (fig. 7a–b). This has been especially true for patients treated by proton beam pituitary irradiation. Although a few patients showed unexplained remission of proliferative retinopathy after pituitary ablation in the absence of clinical hypopituitarism (fig. 6a–b), the majority of patients with incomplete ablation showed several months after irradiation or surgery a gradual transformation of the new vessels into active fibrous tissue with "leakage" and a persistence of the "diffuse microangiopathy." Some of these patients have ultimately gone into the stage of quiescence, whereas in others we observed new areas of neovascularization.

DISCUSSION

Normal retinal vessels have a remarkable endothelial wall, being impermeable even to substances of small molecular weight like fluorescein (*11*). The stimulus for the appearance of neovascularization is

a

b



FIGURES 4 a–d.—*Twenty-eight-year-old male with diabetes for 27 years. New vessels from disc with active diffusion (a), show slight decrease in "leakage" 3 weeks after surgical hypophysectomy (b). Six weeks after ablation "diffuse angiopathy" still persists and new vessels are still visible, but show no "leakage" (c). Twenty months after hypophysectomy marked improvement in neovascularization and angiopathy (d).*

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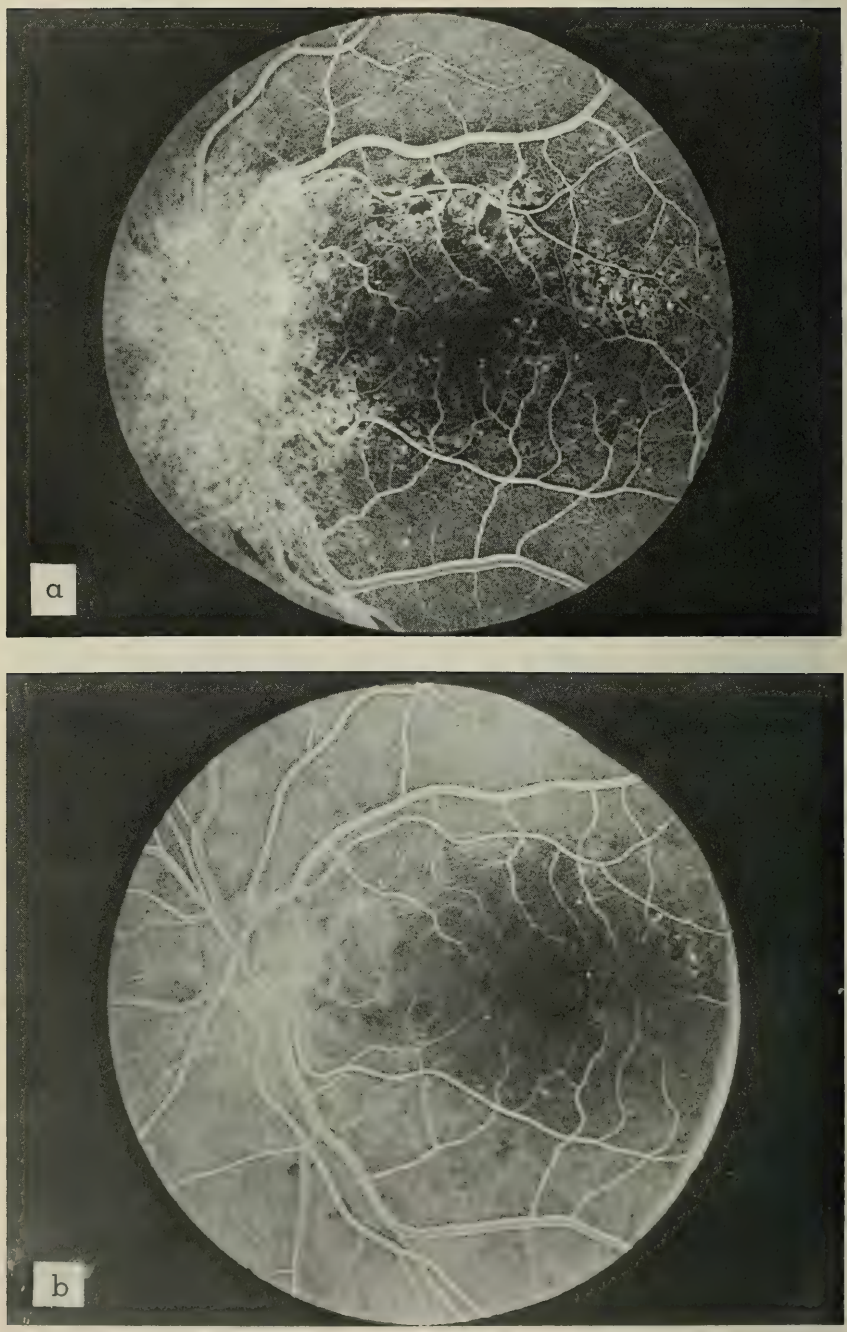
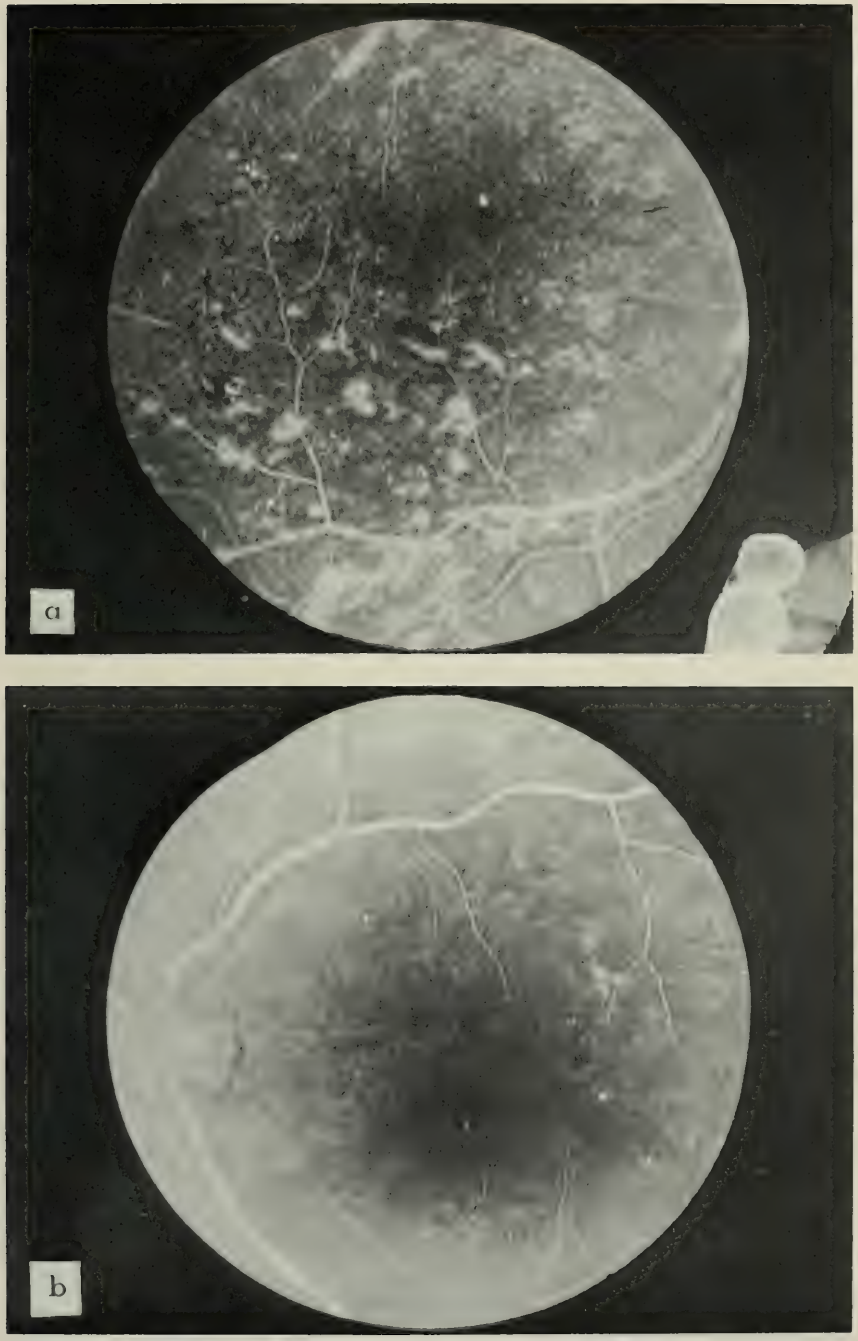
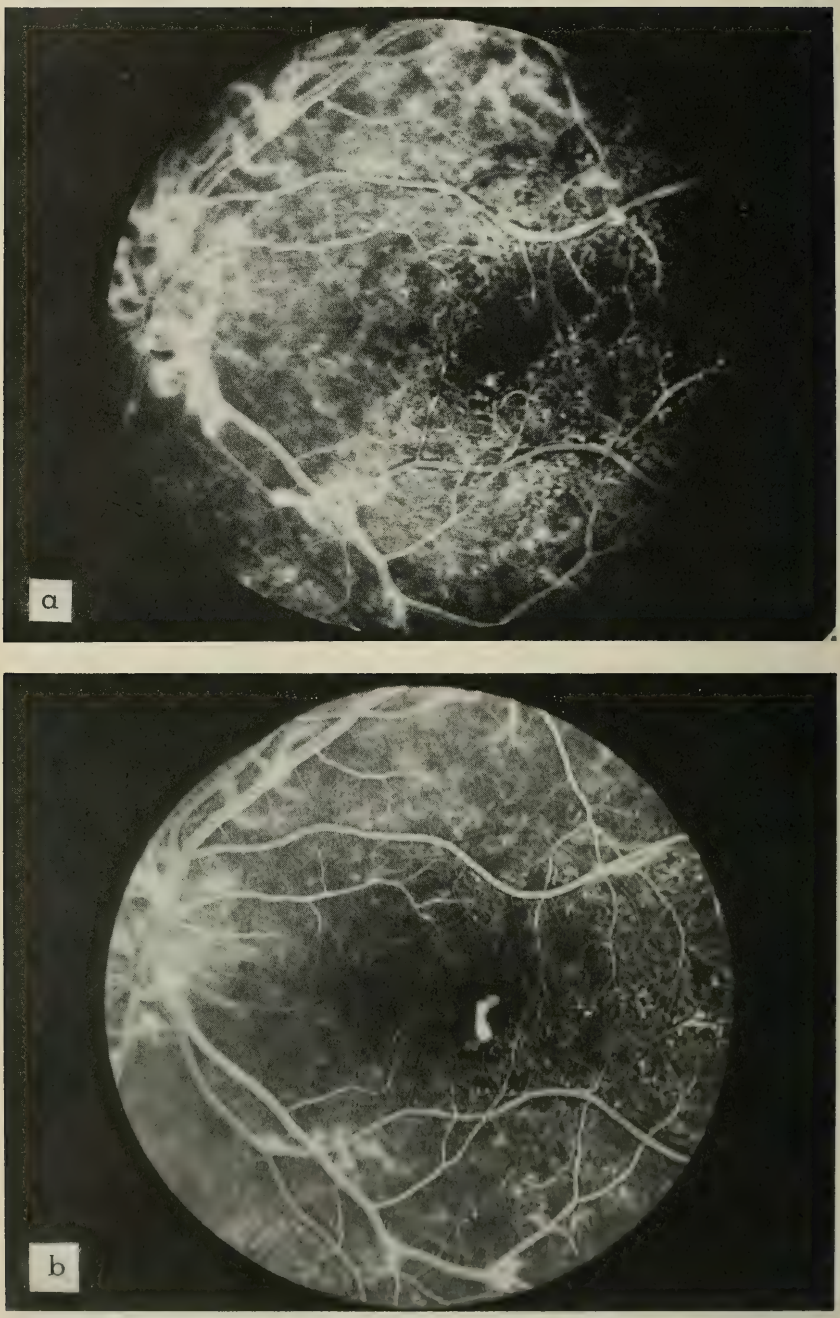


FIGURES 5 a–b.—*Neovascularization from disc and "diffuse angiopathy" (a), show considerable regression 5 months after surgical hypophysectomy (b) in this 36-year-old male with diabetes for 13 years.*



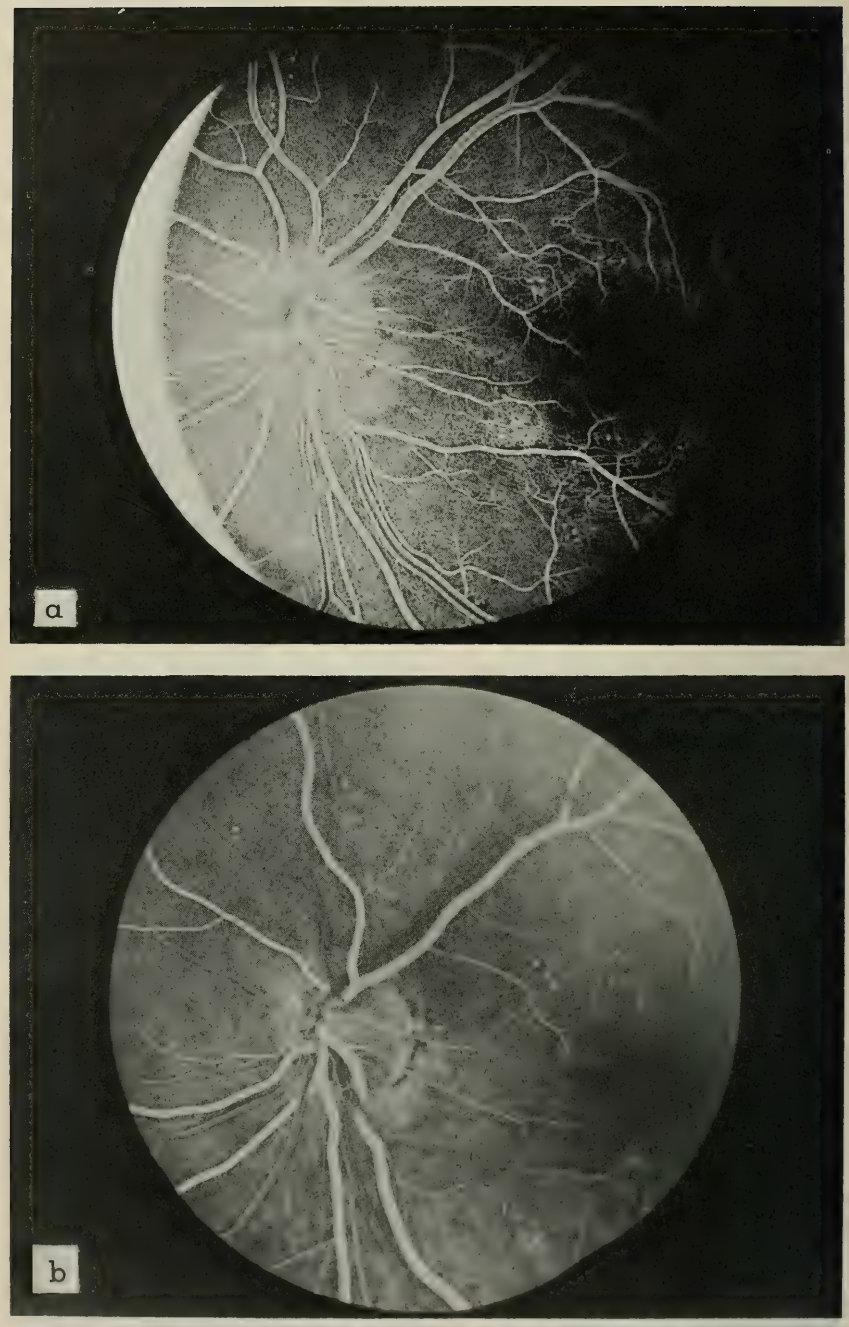
FIGURES 6 a-b.—*Female age 24 years, diabetes 14 years. "Diffuse angiopathy" and areas of "leakage" (a) were improved after pituitary ablation, despite persistence of endocrine target gland function (b).*



FIGURES 7 a–b.—*New vessel formation with "leakage" and "diffuse angiopathy" (a) are only partially arrested 1 year after proton beam irradiation (b) in this 28-year-old woman with diabetes for 11 years.*

FIGURE 8.—*Multiple drusen in a patient without diabetic retinopathy.*

FIGURE 9.—*Arrested case of proliferative retinopathy. Inactive fibrous band does not show fluorescence.*



FIGURES 10 a–b.—*Female, age 18, diabetes 17 years. Early new vessel formation and "diffuse angiopathy" (a) have practically disappeared 11 months after surgical hypophysectomy (b).*

not known. It is evident, however, that new vessels lack the characteristics of normal retinal vessels and show a considerable permeability to fluorescein, a possible forerunner to the all too well known preretinal and vitreous hemorrhage. The "diffusion" properties of the new vessels can be used to a great advantage in the study of fluorescein angiograms. Any therapeutic modality applied to these vessels including pituitary ablation, should influence both their appearance and their functional characteristics if it is to be successful.

The pattern of "diffuse angiopathy" on fluorescein photographs shows a remarkable improvement after pituitary ablation. A similar improvement has been obtained with other forms of therapy, including strict regulation of diabetes in a previously uncontrolled patient. Dollery and Oakley (*23*) demonstrated with color and fluorescein photographs a remarkable remission of diabetic retinopathy in a 14-year-old girl treated only by means of strict control of diabetes with diet and insulin. "Diffuse angiopathy" may represent "functional" reversible vessel changes and may be related to abnormal circulating plasma fractions, renal disease, retinal edema or other pathologic elements.

The disappearance of the multiple microaneurysms may be viewed as a progression to a thrombosed or hyalinized, nonpatent aneurysm rather than restitution to a normal vessel. It remains unresolved whether the dilated capillaries lying flat on the retina in "diffuse angiopathy" represent vessels produced *de novo* or dilated preexisting capillaries and vascular shunts, as indicated by histologic observations in diabetic retinopathy (*24*).

From the above considerations it is apparent that fluorescein photography of the retina is particularly suited to the study of the angiopathy in proliferative diabetic retinopathy. It provides better understanding of the relationship of specific abnormalities to the multiple factors responsible for the progression of proliferative diabetic retinopathy and helps in evaluating therapy and prognosis. Fluorescein angiography may be of help in the selection of patients considered for hypophysectomy. Documentation of the eye status in such individuals by fluorescein photography is desirable, inasmuch an angiopathy appears to be the pathologic element primarily affected by pituitary ablation.

In conclusion, fluorescein angiography of the retina provides the clinician with an *in vivo*, nontraumatic technique of visualization of pathophysiologic events and changes in the retina which cannot be obtained by conventional ophthalmoscopic or histologic methods. In addition to the anatomic and structural changes of the retinal vascular tree, the newer techniques of fluorescein angiography and cineangiography may give us information concerning retinal hemody-

namics (*25*) and help to explain the pathogenesis of neovascularization.

Acknowledgment

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SUMMARY

Sixty patients with proliferative diabetic retinopathy who underwent pituitary ablation by surgical procedures or proton beam irradiation were studied one or more times with fluorescein photography of the retina.

Many true microaneurysms and delicate new vessels can be better demonstrated in these photographs than by ophthalmoscopy or conventional color photography. In active cases of retinopathy the new vessels and the areas of proliferation and connective tissue formation show diffusion ("leakage") of dye and persistent glow. After successful pituitary ablation the "leakage" decreases and stops, the new vessels involute and disappear, and the characteristic pattern of "diffuse angiopathy" returns toward normal.

Fluorescein photography of the retina is a useful, nontraumatic method for serial *in vivo* observations in diabetic patients.

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CHAPTER 17

Surgical Pituitary Ablation for Diabetic Retinopathy

ROBERT F. BRADLEY, M.D.
SEARLE B. REES, M.D.

Earlier data concerning the effects of surgical pituitary ablation upon the course of retinitis proliferans [1] in the diabetic patient revealed the following: (1) Stabilization or improvement in visual status and/or the funduscopic findings occurred with greater frequency than was anticipated from observations of the natural course of this disease (*1*); and (2) Pituitary stalk section was apparently less reliable than total hypophysectomy in producing a reduction in retinal microangiopathy and cessation of retinal or vitreous hemorrhage (*2*). Review of the rationale for pituitary ablative procedures, proposed mechanisms for their effect upon diabetic retinopathy, results in terms of effects upon visual status and the patient as a whole, the reported necessary degree of hypopituitarism, and comparisons of the effects of pituitary ablation with the natural course of retinitis proliferans were tabulated 3 years ago (*1*) and have been recently summarized (*3*).

In view of the variable course of hemorrhagic retinal angiopathy, evaluation of a suitable "control" group is clearly desirable—patients who are treated, except for pituitary ablation, in the same manner as the operated group. Earlier, this was done by comparing 39 patients treated medically with 33 patients undergoing pituitary stalk section or subtotal hypophysectomy (*2*). In the former, vision improved in three and retinopathy was "arrested" in eight, whereas vision improved in 17 and retinopathy was arrested in six of the operated individuals. The average followup interval for both groups was only 14 months. For one reason or another, it became increasingly difficult to maintain patients in the "control" group, so that valid comparisons are not at present available from our own experience.

The observations which follow summarize results with surgical pituitary ablation in 87 diabetic patients with hemorrhagic retinopathy accompanying proliferative angiopathy. The pituitary ablative procedures were performed during the years 1961–1966, thus

From the Joslin Clinic and the Elliott P. Joslin Research Laboratory of Diabetes Foundation, Inc., and the Department of Medicine, Harvard Medical School. This investigation was supported in part by USPHS grant AM–04146 and the Massachusetts Lion's Eye Research Fund.

[1] The term "retinitis proliferans" is subsequently avoided because some observers restrict its use to the fibrous component of proliferating retinopathy.

giving opportunity for minimum followup observations of 2 years. Both early and later eye failure could be evaluated, as well as limitations upon long-term survival among these diabetic patients, whose general condition is significantly affected by generalized microangiopathy, neuropathy, and/or atherosclerotic disease. In addition, the degrees of hypopituitarism resulting from pituitary stalk section and subtotal or total hypophysectomy have been assessed in many patients and correlated with apparent benefits in terms of vision and cessation of retinal angiopathy or hemorrhage.

PATIENTS

The 87 treated patients comprised five from the Lahey Clinic and 82 from the Joslin Clinic Services, for whom approximately the same criteria were used in selecting the patients for surgery, which was performed in all instances by Dr. Charles Fager, with the exception of three patients operated by Dr. Donald Matson.[1] The characteristics of the patients were comparable to those found in other series; namely, an average age of 35 years with average known duration of diabetes 20 years, and the striking, as yet unexplained ratio of two males to one female.

With few exceptions, the individuals as a whole were characteristic of those in whom proliferating retinopathy is increasingly found, i.e., following 10 to 25 years of insulin-dependent diabetes with onset before age 20 (*4*) as shown in table 1. Only four patients in the present series were of the maturity onset type.

OPERATIVE PROCEDURES

Technical aspects of the simple low section of the pituitary stalk and hypophysectomy procedures are described separately by Fager (*5*). Operative mortality was limited to one woman dying in the early portion of this experience (1.1 percent), compared to the overall 8.8 percent found in the combined experience among 387 patients previously recorded in 1965 (*1*).

Simple low section of the pituitary stalk was carried out in 31 diabetic patients (13 females, 18 males). Because hypopituitarism was obviously not induced in one patient and recurring vitreous hemorrhage accompanied apparently inadequate pituitary ablation in sev-

[1] Dr. Donald D. Matson, Peter Bent Brigham Hospital, Boston.

TABLE 1.—*Surgical pituitary ablation (1961–66)*

MALIGNANT DIABETIC RETINOPATHY—AUGUST 1968

	Number [1]	Age [2]	Duration diabetes [2]
Males	57	20–60 (37)	4–39 (22)
Females	30	18–47 (31)	11–31 (19)
Total	87	18–60 (35)	4–39 (21)

[1] 4 males excluded from averages because of known diabetes plus or minus 1 year (maturity-onset type).
[2] At time of surgery.

eral additional patients, a portion of the pituitary was excised along with the hypophyseal end of the pituitary stalk following very low section, in order to produce at least moderate pituitary insufficiency. This procedure was carried out in 13 individuals (five females, eight males) and is subsequently referred to as "subtotal hypophysectomy." Again, nearly intact pituitary function persisted in at least two women, associated with recurring vitreous hemorrhage and persistent activity of the angiopathy. All subsequent operated patients were subjected to procedures rated as "questionably total" (two females, three males) or "total hypophysectomy" (nine females, 27 males). Preliminary observations in the latter group appeared to indicate that the more total hypopituitarism produced in most instances was associated with more rapid disappearance of hemorrhage and regression of new vessel formation in the fundi (*2*). The early impression that minimal pituitary ablation was inadequate was fortified by observations in two diabetic men who had undergone heavy particle irradiation of the pituitary [1] with only minimal evidence of suppression of pituitary activity and no effect in suppressing the angiopathy or hemorrhage in the eyes. These men subsequently underwent total hypophysectomy followed by maximal hypopituitarism with an excellent effect upon the eyes in one and failure in the other.

Of five women and two men in whom stalk section or subtotal hypophysectomy failed to produce maximal hypopituitarism and in whom retinal angiopathy was inadequately suppressed, further treatment was given using heavy particle irradiation to the pituitary.

METHODS

A simplified protocol was adopted for pre- and post-operative evaluation of the eyes, general condition, and endocrinologic status. This

[1] Dr. Raymond N. Kjellberg, Proton Beam Biomedical Annex of Harvard Cyclotron Laboratory.

was based upon principles outlined by Field and his associates (*6*), so that comparable data might be obtained. General evaluation was directed toward detection of previously unrecognized disease, diabetic neuropathy and nephropathy, remediable sources of hypertension, coronary heart disease, and atherosclerotic involvement of cerebral and peripheral blood vessels.

Eye Evaluation

Visual status and detailed description of the components of retinopathy were reported by ophthalmologists thoroughly familiar with diabetic retinopathy, in the majority of patients by Dr. William P. Beetham.[1] Fundus photographs were obtained in all instances wherein good technical results could be expected. Whenever possible, postoperative evaluation was performed by the same ophthalmologist and by repeat fundus photography. In 38 patients, additional assessment of retinal angiopathy and the degree of leakage of blood from retinal vasculature was evaluated by means of fluorescein angiography (*7*).

Opportunity for detailed evaluation of retinopathy components before and at varying intervals after surgery according to the classification adopted for this symposium has been inadequate to allow valid recording of the necessary information. Much of the description of the eye changes took place some time in the past and represented overall assessment of changes in neovascularization, cessation of hemorrhage, degree of fibrous tissue formation, etc.

Endocrinologic Evaluation

In all patients considered to be potential candidates for pituitary ablation, tests of pituitary target organ function were performed. These included protein-bound iodine, radioactive-iodine uptake, basal metabolism, 24-hour excretions of 17-ketosteroids and hydroxycorticosteroids, urinary FSH, and in some instances urinary steroid excretion following the administration of metapyrone.

In all instances, the nature of the problem, including orientation of the patient and his nearest responsible relative concerning the natural course of hemorrhagic retinopathy, was defined by one of the authors and/or by the responsible Joslin Clinic physician. Particular care was taken to stress the possibility of spontaneous remission of the retinopathy, the possible adverse effects of pituitary ablation, and

[1] The ophthalmologists performing these examinations were Drs. William P. Beetham, John P. Hill, J. Wallace McMeel, and Alfred W. Scott.

the need for responsible care by the patient and his nearest relative of the potential metabolic problems, especially those related to the handling of insulin and adrenal steroids. In some instances, formal psychiatric evaluation was utilized in guiding decision as to adequate emotional stability of the patient.

A program of conservative medical management was outlined for each individual as a basis for evaluating the possibility of spontaneous reversibility of the retinal pathology. These measures were directed primarily toward improved control of the diabetes with avoidance of severe hypoglycemia, minimizing all types of stress that might increase ocular intravascular pressure, control of diastolic hypertension, and eradication of infection, with emphasis upon that involving the urinary tract. Details of such management are presented elsewhere (*1*).

CRITERIA FOR SELECTION OF PATIENTS

In an effort to avoid subjecting any individual to pituitary ablation unnecessarily, diabetic patients were usually selected at the stage when only one potentially salvageable eye remained, in which retinal angiopathy or hemorrhage could be shown to be worsening despite a reasonable degree of adherence to the program of conservative medical management. Earlier selection would be more likely to yield better results from an eye standpoint, but pituitary ablation was delayed until there was certainty that stabilization or remission of the retinopathy was not occurring.

The general criteria were related to ensuring that the patient would have an excellent chance of surviving the operative procedure and thereafter long enough to reap some benefits of preserved vision. The great importance of this consideration has been pointed out by subsequent studies indicating extraordinarily limited survival in many patients once these advanced degrees of retinopathy have developed.

The following retinal and general criteria were carefully followed in most instances. In some, however, the decision to proceed with pituitary ablation was undoubtedly ill advised, particularly for those in whom there was evidence of diminution of renal function, persistent diastolic hypertension, or coronary heart disease.

Retinal Criteria

1. Progressive retinopathy occurring at a rate such that loss of useful central vision is threatened within a relatively short, predictable period of time; i.e., a few months to 1 year. Documentation of such

progression should be obtained by objective recording of fundus changes by means of retinal photography and/or mapping (*8*).

2. Proliferating angiopathy with or without fibrosis and active recurring hemorrhage were acceptable provided at least one macular region was intact or the changes in this area potentially reversible, such that useful vision in at least one eye could be attained assuming the hemorrhagic tendency and further fibrotic change were halted by pituitary ablation.

In most instances, patients have progressed to the point that one eye is destroyed and macular vision in the remaining eye has either been intermittently impaired by vitreous hemorrhage or threatened by neovascularization and collagen formation. In a few instances, macular vision has been intact in both eyes, but either recurring vitreous hemorrhage or the degree of neovascularization appeared to threaten the macular regions simultaneously.

3. Contraindications to a pituitary procedure warranting postponement or elimination as a candidate have consisted of bilateral, complete, irreversible macular destruction or deterioration to the point that useful vision could not be restored; massive vitreous bleeding making adequate view of the macular regions unobtainable; or retinopathy of a type, location, and rate of advance such that involvement of the maculae has not been occurring or has developed at a very slow rate. The need for continued observation of such patients is obvious, as the rate of progression may change or vitreous hemorrhage might clear, revealing an intact macula in one or both eyes. Conditions then found might indicate surgical intervention.

4. In all instances, the opinion of an ophthalmologist, not only competent, but also experienced in observation of the course of diabetic retinopathy, should be obtained.

General Criteria

General factors of importance must be evaluated in the light of their effect upon the patient's ability to survive the considerable metabolic changes associated with the surgical induction of hypopituitarism and to live long enough to allow the benefits of retained vision to be worthwhile, and also to permit evaluation of the possible influence of these factors upon the course of retinopathy during hypopituitarism. The following findings were probable reasons for eliminating a patient as a candidate:

1. Clinical evidence of significant nephropathy, including (alone or in combination) endogenous creatinine clearance consistently below 40 milliliters per minute per 1.73 square meters of body surface, serum creatinine 2.0 milligrams per 100 milliliters or more, proteinuria in

excess of 4 grams per 24 hours, serum albumin below 3.0 grams per 100 milliliters, or refractory urinary tract infection.

Renal biopsies were obtained prior to pituitary ablation and at intervals postoperatively to assess changes in ultrastructure associated with pituitary ablation and to rule out any remediable nondiabetic cause of renal failure. Earlier the renal biopsy was also used as a guide to selection of patients for pituitary ablation, but of late such morphologic criteria have been eliminated.

2. Fixed cardiomegaly or arrhythmia, extensive or recent myocardial infarction, overt or borderline cardiac failure, or angina pectoris. In some instances, Joslin Clinic patients have been accepted despite the presence of angina pectoris if infrequent or requiring considerable stress for its demonstration.

3. Chronic, ineradicable infection anywhere.

4. Incapacitating peripheral or visceral neuropathy, particularly the presence of postural hypotension, difficulty with which is distinctly enhanced following pituitary ablation and often presents a serious problem postoperatively.

5. Persistent diastolic hypertension of 100 millimeters of mercury or more has appeared to be associated with a greater incidence of postoperative azotemia and a persisting hemorrhagic tendency in retinal blood vessels despite the presence of hypopituitarism. Hypophysectomy usually induces an immediate decrease in renal blood flow and glomerular filtration rate, presumably as a result of eliminating the renotrophic effects of growth hormone, a phenomenon established in the early studies of Luft et al. (*9*), Sjögren, (*10*), and Teuscher (*11*). Not infrequently diabetic patients with borderline renal function prior to induction of pituitary insufficiency will after surgery show a fall in creatinine clearance and even the development of azotemia. However, the decrease in renal function is not continuous. Indeed, one hopes that the possible beneficial effects of hypopituitarism upon the microvasculature of the retina will also play a role in arresting or halting the rate of progression of similar changes in the renal parenchyma. To date, available biopsy data before and after artificially induced hypopituitarism is insufficient to prove this point one way or the other.

6. A mature adjustment of the patient to his illness and a supportive patient-physician relationship is absolutely essential before considering a radical pituitary ablation. Intelligence, emotional stability, and capacity to develop trusting relationships are vital to the demands of a well-ordered regimen including medication, diet, and regular followup examination. The patient's increased sensitivity to insulin and dependence upon adequate steroid replacement which may vary with stress,

333-611 O—69——14

etc., necessitate close observation by a competent spouse, parent, sibling, and/or friend who has an intimate and concerned relationship. Motivation for pituitary ablation must be carefully evaluated with resolution of any unrealistic expectations and relevant conflicts. Similarly, the patient threatened with blindness must weigh the assets, liabilities, and limitations of pituitary ablation before making his own decision. Diminished libido, infertility, and increased dependence upon supervised replacement therapy must be considered in the light of the patient's needs and defenses for optimum adjustment to diabetes which could be complicated by blindness despite pituitary ablation. Reduction of insulin requirements and susceptibility to ketosis are minimal assets if the patient cannot prevent severe insulin reactions in the presence of increased insulin sensitivity, which complicates all cases of insulin-dependent diabetes following ablation of pituitary function.

Thus, diabetic patients selected for pituitary ablation require exceptional insight and further education to help in regulating diet, exercise, insulin, and hormone replacement therapy postoperatively. In the experience of the Joslin Clinic, the ideal candidates for possible pituitary ablation have required 3 or more months of careful supervision, evaluation, and instruction before decision for definitive therapy was reached. In some cases, the improved total patient care which resulted from this intensive preparation and followup eliminated the need for pituitary ablation; with few exceptions only patients who demonstrated progression of hemorrhagic retinitis proliferans despite 3 to 6 months of optimum management were subjected to pituitary surgery. In view of the retinal criteria used as a basis for considering patients as possible candidates for pituitary ablation, it is not surprising that the majority of those evaluated with this in mind showed sufficient progression during the period of observation to place them in the treated group. Those who did not show such progression usually had little or no visual change and tended to be more reluctant to proceed with pituitary surgery. This relatively small portion of the patients evaluated for pituitary ablation were placed in the control series mentioned earlier, thus providing another variable among the "control" patients making them unsuitable for comparison.

MANAGEMENT

Management has been the same for all patients undergoing surgical ablation of the pituitary or by means of stalk section, subtotal or total hypophysectomy. Cortisone acetate, 50 milligrams intramuscularly, is given the night before and repeated the morning of operation, and

usually 100 milligrams intramuscularly is given during the first 12 to 24 hours postoperatively. Thereafter, cortisone dosage has been tapered rapidly over the next 5 to 6 days to 37.5 to 50 milligrams daily and finally to between 25 and 37.5 milligrams daily at the time of discharge. In some instances, the neurosurgeon may add large doses of parenteral dexamethasone in order to minimize cerebral edema. Dilantin is given intramuscularly in all patients to prevent seizures. By means of utilizing smaller doses of cortisone and tapering it rapidly, the problem of postoperative diabetes insipidus is minimized, and only rarely has Pitressin administration been necessary in our experience. A few patients have had polyuria and increased water intake without symptomatic discomfort, requiring Pitressin administration for periods of no more than 3 to 6 months.

Because of rapid reduction in pituitary function with surgical ablation, insulin antagonism and synthesis of ketoacids are reduced so that less insulin is necessary than in the usual diabetic individual receiving comparable dosages of steroid replacement. Postoperative polydipsia and polyuria are significantly diminished when cortisone replacement and filtered loads of glucose, salt, and water are physiologic. The administration of a steroid makes it quite safe to utilize the usual dosages of long-acting insulin on the day of surgery and for 1 or 2 days thereafter, supplemented by crystalline insulin in small amounts. With lowering of steroid dosage, insulin must be sharply reduced with the expectation that final insulin dosage may be as little as one-quarter to one-half the preoperative requirements.

Liquid to soft diet can be tolerated in most instances within a day or two after surgery. As adrenal function lessens and steroid administration is tapered, sodium losses in the urine increase and salt intake must be liberalized by the fourth or fifth day postoperatively to prevent depletion. Postural hypotension can be a significant problem postoperatively, particularly in those patients who have demonstrated this manifestation of diabetic neuropathy preoperatively. Usually a liberal salt intake utilizing bouillon three or four times a day replaces deficits and prevents hypotension, but on occasion 0.1 to 0.2 milligrams of 9-alpha-fluorohydrocortisone in divided dosage may be required. At times, pronounced hyponatremia and anemia with central nervous system signs suggesting cerebral edema were probably due to water retention, as suggested by others (*12*, *13*). In such instances, water restriction has also been necessary.

In an effort to maintain a hypometabolic state postoperatively and thus possibly increase the chance of halting further progression of retinopathy, the custom has been to withhold thyroid or gonadal replacement therapy until symptoms experienced by the patient have required treatment, usually after 6 months or longer.

On discharge, patients are given the usual diabetic diet with somewhat fewer calories to avoid excessive weight gain and in most instances with liberal added salt, the reduced insulin dosage established in the hospital before discharge, cortisone 12.5 to 25 milligrams in the morning and 5.0 to 15 milligrams at night, and occasionally 9-alpha-fluorohydrocortisone for those patients whose postural hypotension has not been adequately controlled by liberal salt intake. Many patients who prior to surgery required a split dose of intermediate-acting insulin could be managed postoperatively with intermediate-acting insulin alone or supplemented by tiny doses of crystalline insulin given once daily. In all instances, a responsible relative is thoroughly instructed in the use of glucagon and also of intramuscular cortisone in the event the patient is unable to take cortisone by mouth. Furthermore, patients are instructed to maintain the program of conservative management learned during the observation phase prior to operation, at least until retinal angiopathy and hemorrhage appear to have subsided.

Despite instructions to the patient and a responsible relative, in most instances supplemented by written instructions, experience has been that over a period of weeks and months the easy production of significant hypoglycemia and/or adrenocortical insufficiency are forgotten. The usual tendency for the well-trained diabetic patient during acute illness associated with nausea, vomiting, and fever has been to remember the principles of caring for the diabetes, only to forget the urgent need for receiving replacement or supplemental steroid therapy.

RESULTS

The characteristics of the diabetic patients related to vascular disease and neuropathy are indicated in tables 2 and 3. One male died of myocardial infarction following pituitary stalk section less than 2 months after surgery. One woman died in the immediate postoperative

TABLE 2.—*Preoperative complications (pituitary ablation)*

	Proteinuria	↑ BUN [1]	↓ Renal function [2]	Hypertension [3]
Males	31	4	6	36
Females	11	0	0	12
Total	42	4	6	48

[1] Creatinine persistently elevated in only 1.
[2] Endogenous creatinine clearance <40 mL/min. in only 2.
[3] More than 1 diastolic blood pressure >90 mm. Hg.

TABLE 3.—*Preoperative complications (pituitary ablation)*

	Neuropathy	Postural hypotension	Coronary heart disease	Peripheral vascular disease
Males	Majority	12	3	6
Females	do	5	0	0

period of intracerebral hemorrhage after pituitary stalk section. Later observations are based upon evaluation of the remaining 29 women and 56 men. Followup intervals range from 7 to 84 months, average 44 months for males and 47 months for females. Except for one male, all patients have been followed to within the last year with data available in most patients to August 1968.

The preoperative status of patient eyes is indicated in tables 4 and 5. Note the significant majority (70 out of 85 patients) with only one or no eyes considered salvageable. Of those with both eyes at risk, only two—both females—had intact vision O.U.

Assessment of residual pituitary function postoperatively has been crude at best, but data concerning the following manifestations of pituitary function have been adequate in most instances to arrive at a rough appraisal:

(*a*) *Insulin dosage*—Changes in insulin dosage were of value in 50 out of the 56 men. Two were not taking insulin prior to surgery and

TABLE 4.—*Surgical pituitary ablation (1961–66)*

EYES AT RISK [1]

	None (blind or <20/200 in better eye)	O.S.	O.D.	O.U.
Females	4	9	11	5
Males	3	20	23	10
Total (85)	7	29	34	15

[1] For all survivors (29 females, 56 males) of the postoperative period.

TABLE 5.—*Surgical pituitary ablation (1961–66)*

EYES AT RISK [1]

	None (blind or <20/200 in better eye)	O.S.	O.D.	O.U.
Females	4	9	11	5
Males	2	16	18	9
Total (74)	6	25	29	14

[1] For survivors (29 females, 45 males) of the postoperative period and followed for 1 year or longer at time of initial evaluation in May 1967.

an additional four probably did not require insulin. Of the women, only one did not require insulin. Preoperative insulin dose was determined only after the diabetes was stably regulated and was compared with the postoperative insulin needs with individuals on a comparable diet. Reduction in insulin need to one-half or less of the preoperative amount was considered significant.

(*b*) *Menses*—Changes in menstruation could be utilized in all women except for one who had undergone previous hysterectomy, as the remaining 28 women were menstruating preoperatively. Of these 28 women all except four had complete and lasting cessation of menses. Of the four, two became pregnant, resulting in one spontaneous abortion and one live baby.

(*c*) *Thyroid*—Considerable variation in degrees of thyroid suppression following pituitary ablation was noted. Complete suppression of thyroid function by all parameters measured was attained in a total of only 45 patients and partial supression in 33. Thyroid function was either normal or only temporarily reduced in six patients.

(*d*) *Adrenal*—Excretions of adrenal steroids have been evaluated in only a few patients postoperatively and thus have been of little assistance in estimating the degree of hypopituitarism. However, 12 men and 10 women experienced classic episodes of acute adrenal insufficiency, and questionable episodes occurred in two additional men. Repeated episodes occurred in two of the men and two of the women.

(*e*) *Growth hormone*—Circulating growth hormone before and after insulin induced hypoglycemia (*14*) has been measured in 44 patients at varying intervals, 2 years or more postoperatively. Of the 32 showing no rise in growth hormone following hypoglycemia, 29 were rated as having "moderate" or "maximal" pituitary ablation based on reduction in insulin dose and cessation of menses, and two were considered to have only slight hypopituitarism by these parameters. Of these two, one man had partial suppression of thyroid function and one episode of adrenococortical insufficiency, and the one women was rated as having moderate to complete pituitary suppression by all parameters except for a persistently elevated insulin dose. Of the total group, thyroid function was low by all measurements in 20 patients and at least partially suppressed in 12.

Of those seven individuals with low levels of circulating growth hormone after hypoglycemia, all were rated as having "moderate" to "maximal" pituitary suppression on the basis of change in insulin dose and cessation of menses.

Of the five persons with normal circulating growth hormone following hypoglycemia, four were rated as having incomplete or no hypopituitarism on the basis of lack of change in insulin dose and per-

sistence of menses, and one female was considered to have moderate to maximal pituitary ablation on the basis of these factors.

A somewhat arbitrary overall assessment of the degree of hypopituitraism has been determined as listed in table 6. Resulting degrees of hypopituitarism for the operative procedure performed are summarized in table 7. Review of this data reveals that hypophysectomy does not guarantee hypopituitarism, as little or no pituitary ablation was apparent in one female and one male following this procedure. It was also apparent that hypophysectomy has resulted in grade III hypopituitarism in more patients that was noted after the other procedures. Despite this trend, further comparison of pituitary stalk section and hypophysectomy (table 8) indicates that the number of patients with "little or no" pituitary ablation following either procedure was minimal and that on combining those having "moderate" or "maximal" hypopituitarism no difference between the procedures could be detected.

POSTOPERATIVE EYE STATUS

At the time of the first available and reasonably complete evaluation of eye status of the total series of patients in May 1967, after elimination of one woman and one man dying in the postoperative

TABLE 6.—*Surgical pituitary ablation*

DEGREE OF HYPOPITUITARISM

Rating	Degree	Criteria
I	Slight or none	Insulin greater than ½ preoperative dose. Thyroid function normal. Absence of adrenal insufficiency. Persisting menses. Normal growth hormone response to hypoglycemia.
II	Moderate	Insulin less than ½ preoperative dose. Thyroid function variably suppressed. Adrenal insufficiency plus or minus. Menses absent. Minimal or no growth hormone response to hypoglycemia (1 exception).
III	Maximal	All criteria in "moderate" plus thyroid function persistently low by all tests. Adrenal insufficiency plus or minus.

TABLE 7.—*Operations and resulting hypopituitarism*

Procedure	0–I			II			III			
	Females	Males	Total slight or none	Females	Males	Total moderate	Females	Males	Total maximal	Total procedure
Pituitary stalk section	1	2	3	9	8	17	3	8	11	31
Subtotal hypophysectomy	2	0	2	3	3	6	0	5	5	13
Total hypophysectomy	0	0	0	2	1	3	0	2	2	5
Hypophysectomy	1	1	2	5	7	12	3	19	22	36
Total	4	3	7	19	19	38	6	34	40	85

TABLE 8

Operative procedures	Number	Degrees of hypopituitarism			
		I slight	II moderate	III maximal	Total II + III
Stalk section	31	3	17	11	28
Hypophysectomy	36	2	12	22	34

period, as well as an additional 11 men followed for less than one year, 74 patients remained (29 females, 45 males). Six patients were rated as having "no eyes at risk" because of visual acuity in the better eye of less than 20/200. These individuals were subjected to operation because the underlying macula had recently been noted to be intact in at least one eye.

Summary of the evaluations of visual results in patients for whom data was available for twelve months or more is indicated in table 9. The results are pessimistic because of the following: (*a*) patients with two eyes at risk are rated as failure if the results in one eye are poor regardless of improvement or stability in the other; (*b*) all patients with improvement or stability in at least one eye for 12 months are considered as failures if the eye later regresses no matter how slight the regression may be or the length of the interval before it occurred; and (*c*) patients with no eyes at risk were considered as failure unless significant improvement occurred in at least one. Such developed in only one woman out of four and none out of three men.

Note that the criteria for assessment of patients as improved or stable rather than failure significantly alters the degree of success, as indicated in table 10. Thus, the salvage of one eye in a two-eyed patient, stability or improvement for at least 12 months despite some degree of later failure in an eye at risk, and improvement in an eye opposite

TABLE 9.—*Pituitary ablation*

DEGREE OF HYPOPITUITARISM AND VISUAL RESULTS—29 FEMALES, 45 MALES, JUNE 1967

	Improved or stable			Failure			Percent improved or stable
	Females	Males	Total	Females	Males	Total	
I. Slight or none	1	1	2	3	1	4	33
II. Moderate	11	5	16	8	10	18	47
III. Maximal	4	13	17	2	15	17	50
Total	[1] 16	[2] 19	35	13	26	39	47

[1] 16 of 29 females, improved or stable.
[2] 19 of 45 males, improved or stable.

the one at risk are compatible with rating "improved or stable," yielding 70 percent as opposed to 50 percent favorable results.

Of the five women and two men later having heavy particle irradiation of the pituitary (10,000 to 14,000 rads), persistent proliferative angiopathy and/or recurring eye hemorrhage had occurred in all of the women and one of the men. In the other man, maximal hypopituitarism had already been attained and a decrease in vision was due to detachment of the retina at the macula, both eyes having shown marked regression of angiopathy and cessation of all hemorrhage. In three of the women, either slight or no hypopituitarism had occurred following surgical pituitary ablation and in two of these no further evidence of hypopituitarism has been noted following pituitary irradiation. In one of these, pituitary ablation was finally rated as maximal after a period of 9 months and was associated with complete cessation of angiopathy and hemorrhage, which had persisted following the previously inadequate pituitary stalk section. The remaining two women were subjected to heavy particle irradiation of the pituitary because of recurring eye hemorrhage, although hypopituitarism was already rated as moderate to maximal in both. The degree of hypopituitarism was not significantly changed in these two women following irradiation. Recurring eye hemorrhage was a persistent problem for a time after this procedure, although subsequent complete clearing occurred.

Subsequent Visual Course

In an effort to determine the rate at which visual change might be occurring, a subsequent evaluation of visual status carried to August 1968 has yielded later information in the majority of surviving patients. This includes further data in the 11 men who were excluded

TABLE 10.—*Pituitary ablation*

DEGREE OF HYPOPITUITARISM AND VISUAL RESULTS [1, 2]— 29 FEMALES, 45 MALES, JUNE 1967

	Improved or stable			Failure			Percent improved or stable
	Females	Males	Total	Females [3]	Males	Total	
I. None or slight	2	1	3	2	1	3	50
II. Moderate	14	10	24	5	5	10	71
III. Maximal	5	20	25	1	8	9	74
Total	21	31	52	8	14	22	70

[1] Patients with 2 eyes at risk are rated as improved or stable on the basis of findings in 1 eye despite failur e of the other.
[2] Stability or improvement for a minimum of 12 months in at least 1 eye regardless of later failure.
[3] 1 female rated improved because poor eye improved significantly although better eye failed.

from the 1967 results. Three of these died less than 12 months after pituitary ablation. The remaining eight added to the original 74 patients yield information regarding the eyes after at least 12 months in 82 of the original 87 patients. The overall followup intervals in this group range from 13 to 84 months for those living at least 1 year. Of the 74 patients reported less optimistically in table 9 only four changed significantly during the next 12 to 15 months. One woman showed definite increase in neovascularization with recurrent hemorrhage in one eye, the other remaining eye entirely quiet. Another woman had only one eye at risk, in which an increase in new blood vessels with minor hemorrhage occurred without measurable change in visual acuity. In two men, significant increase in angiopathy with hemorrhage and significant loss of vision developed. These changes plus the additions of the eight men whose followup intervals had previously been inadequate yielded results as recorded in table 11.

Applying the more optimistic criteria used in preparing the results in table 10, the data in table 12 again yield more favorable patient results, 66 instead of 42 percent being "improved or stable." Note that the rate of visual failure for this interval in excess of 1 year was quite low. Although the greatest portion of the overall visual failures had earlier been observed to occur during the first year following surgery, these occasional late failures in patients whose retinopathy had been quiescent with retention of useful vision has been disturbing.

Angiopathy and Hemorrhage

Alterations in the degree of neovascular proliferation and hemorrhage were considered as diminished or ceased when no additional neovascular proliferation was found or preexisting new vessels regressed, with diminution or clearing of preretinal and vitreous hemorrhage. These observations are summarized in table 13. Note that in

TABLE 11.—*Pituitary ablation*

POSTOPERATIVE VISUAL STATUS (PERSONS), AUGUST 1968

	Improved or stable			Failure			Percent improved or stable
	Females	Males	Total	Females	Males	Total	
I. Slight or none	1	1	2	3	2	5	28
II. Moderate	11	7	18	8	11	19	49
III. Maximal	3	12	15	3	20	23	39
Total	[1] 15	[2] 20	35	14	33	47	42

[1] 15 of 29 females, improved or stable.
[2] 20 of 53 males, improved or stable.

TABLE 12.—*Pituitary ablation*

DEGREE OF HYPOPITUITARISM AND VISUAL RESULTS [1, 2]—29 FEMALES, 53 MALES, AUGUST 1968

	Improved or stable			Failure			Percent improved or stable
	Females [3]	Males	Total	Females	Males	Total	
I. None or slight	2	1	3	2	2	4	43
II. Moderate	14	13	27	5	5	10	73
III. Maximal	5	19	24	1	13	14	63
Total	21	33	54	8	20	28	66

[1] Patients with 2 eyes at risk are rated as improved or stable on the basis of findings in 1 eye despite failure of the other.
[2] Stability or improvement for a minimum of 12 months in at least 1 eye regardless of later failure.
[3] 1 female rated improved because poor eye improved significantly although better eye failed.

10 individuals failure to visualize the fundi precluded accurate appraisal. This left 75 in whom proliferative angiopathy and hemorrhage could be evaluated with some degree of accuracy. With few exceptions, failure of the angiopathy and persistent significant hemorrhage to subside or regress with sufficient rapidity were predictive of the later failure responsible for the visual failures recorded in table 9. In most instances of persisting angiopathy and hemorrhage, an increase in fibrous proliferation was also noted, whereas this component of the retinopathy was affected much less or not at all despite complete subsidence of the angiopathy and cessation of hemorrhage. In such eyes, the fibrous tissue often was noted to have become thinned and reticulated. In one striking instance, a small retinal separation was produced right at the macula in the better eye, with visual failure.

The less favorable visual results than might be expected on the basis of the majority showing a decrease in retinal angiopathy and hemorrhage was attributable in most instances to further loss of visual function prior to maximal attainment of the latter morphologic changes.

TABLE 13.—*Pituitary ablation*

DECREASE IN RETINAL ANGIOPATHY AND HEMORRHAGE—28 FEMALES, 47 MALES, AUGUST 1968

	Females	Total evaluated	Males	Total evaluated	Percent improved
I. Slight or none	[1] 1	4	1	3	29
II. Moderate	12	18	[2] 11	17	66
III. Maximal	[3] 5	6	17	27	67
Total	18	28	29	47	63

[1] In 1 woman (J.D.) recurrent angiopathy and hemorrhage in the better eye has occurred without altering visual acuity.
[2] Lessening of angiopathy and cessation of hemorrhage with visual recovery in 1 man whose vision regressed in the opposite better eye (E.R.).
[3] Recurrent changes at 71 months after surgery in only 1 eye of a woman with 2 eyes at risk (R.H.).

Photocoagulation

A total of seven males and one female have been subjected to retinal photocoagulation using the Xenon arc [1] because of recurrent bleeding from localized tufts of new vessels which had failed to subside despite apparent stabilization or actual improvement in the remainder of the retinal vasculature. In one female a scleral buckling procedure was performed with excellent results.[2]

COMPLICATIONS

Complications occurring postoperatively are listed as late (table 14) and early (table 15). Worthy of comment are the numerous episodes of acute adrenocortical insufficiency, which in most instances were not severe and responded promptly to intravenous hydrocortisone and fluid replacement. These episodes and the extraordinary sensitivity to insulin, particularly that given as supplementary crystalline, point out the hazards of the hypopituitary state even in individuals previously well trained in the care of diabetes and thoroughly instructed as to hazards and preventive measures.

TABLE 14.—*Pituitary ablation*

POSTOPERATIVE COMPLICATIONS

LATE

Hypoglycemia	No fatality, 2?
With brain damage	1 Female.
Adrenal insufficiency	12 Males, 10 Females, 2?, 3 episodes in 2, 2 episodes in 2.
Hypothyroidism	Late replacement.
Androgen or estrogen	Early or late replacement.
Gonadal	1 live birth, 1 spontaneous abortion, 1 father.

TABLE 15.—*Pituitary ablation (1961–66)*

POSTOPERATIVE COMPLICATIONS

EARLY

Diabetes insipidus	All temporary.
Postural hypotension	Bouillon, 9-alpha-fluorohydrocortisone. Water restriction.
Hyponatremia	
Anemia	
↓ Renal function	

[1] Performed by Dr. Wallace McMeel and Dr. Paul C. Wetzig.

[2] Dr. J. Wallace McMeel.

MORTALITY

Apart from the one female death related to the operative procedure, all 20 subsequent deaths with one exception resulted from underlying severe vascular disease in these long-term diabetic patients, or to the hazards of the hypopituitary state (table 16). With one exception, the two women and eight men dying between June 1967 and August 1968 succumbed as a result of vascular disease.

DISCUSSION

Although a suitable "control" group of patients with hemorrhagic retinal angiopathy could not be maintained in sufficient numbers to serve as a valid comparison for the operated patients, rigorous standards for designating visual results as "improved" or "stable" have minimized the chance of presenting an unduly optimistic picture for the benefits obtained from surgical pituitary ablation. For the degree and activity of the retinopathy at the time of operation, the numbers showing remission appeared to the authors and the ophthalmologists evaluating these patients to be greater than had previously been noted in untreated individuals (*15*). In those who did well, the rate and ultimate degree of improvement were distinctly greater than has been noted in those not undergoing pituitary ablation. The most dramatic improvement occured in two young women with retinal findings characterized primarily by diffuse angiopathy, neovascularization on the retina with little or no fibrous proliferation, and minimal or no vitreous hemorrhage. Other participants in this symposium may confirm the impression that these individuals closely mimic two other young women in whom striking spontaneous remission has been reported (*16*, *17*).

TABLE 16.—*Surgical pituitary ablation (87 patients), 1961–66*

MORTALITY

	Operative	<1 year	Later	Causes [1]	Total	Vision
Females	1	0	5	Coronary 5, 3 to 6 years.	6	Good 4; blind 1.
Males	0	5	10	Coronary 8, 2 months to 6 years; uremia 2, 2 to 3 years; cerebral hemorrhage 1, 1.5 years.	15	Good 6; poor or blind 9.
Total	1	5	15		21	

[1] Two males died elsewhere of ? hypoglycemia. One male died elsewhere of ? adrenal insufficiency. One male died elsewhere of ? pulmonary embolus.

For a variety of reasons, not the least of which was a long period of followup in the vast majority with inconstant intervals of retinal evaluation, an attempt to utilize the classification recommended for this symposium yielded suitable data in too few of the total series for worthwhile analysis by this means.

According to age, the numbers who died within the period of observation appeared to be high, but the survivors have lived 4 years or longer, many with useful vision. The late visual failures due to recurrent exacerbation of angiopathy and hemorrhage numbered only four from 1967 to 1968. Although relatively few, they were particularly disturbing because of their unexpected development after long intervals during which retinal angiopathy and hemorrhage had remained strikingly quiescent and the degree of hypopituitarism appeared to be unchanged.

SUMMARY

1. Surgical pituitary ablation was performed in 87 diabetic patients for hemorrhagic retinopathy. Of the 85 survivors of the early postoperative period, subsequent data concerning visual status and general condition were obtained in the majority to 1968, the average followup interval being 45 months.

2. Vision throughout the period of observation was improved or stable in 35 of 82 patients, or 42 percent, if failure in any eye at risk was regarded as patient failure regardless of how late it may have occurred, and in 66 percent if at least one eye per patient was improved or stable for a minimum of 12 months. Significant decrease in retinal angiopathy and hemorrhage was noted in 47 of 75 patients in whom adequate fundus study could be obtained. Stabilization or improvement in visual status and/or the funduscopic findings occurred with greater frequency and rapidity than was anticipated from observations of the natural course of this disease.

3. "Moderate" or "maximal" hypopituitarism was produced in a large majority of diabetic patients after either pituitary stalk section or hypophysectomy, with a slightly greater frequency of "maximal" hypopituitarism after hypophysectomy.

4. Although too few patients had "slight" hypopituitarism or "none" following surgical pituitary ablation to determine significance, either "moderate" or "maximal" degrees of hypopituitarism appeared to be necessary to attain the benefits listed in 2 above.

5. An overwhelming majority of the 21 deaths resulted from the advanced vascular disease characteristic of long-term diabetes, myocardial infarction being the most common cause.

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CHAPTER 18

Some Technical Observations on Surgical Hypophysectomy in the Treatment of Diabetic Retinopathy

CHARLES A. FAGER, M.D.

Reflecting on a decade of neurosurgical experience with diabetic patients leads to certain inescapable conclusions, but still leaves a number of unanswerable questions. First and foremost, it is surely the prayerful hope of everyone concerned with diabetes and its complications that some better method of treatment or prevention than any of those currently available will be found. In particular, deliberately to superimpose another disease upon the diabetic is far from satisfactory. The grim predicament of hypopituitarism is fearful enough in the nondiabetic, even in this age of so-called substitution therapy. Since it has become all too clear that a more complete hypophysectomy or pituitary ablation is necessary to provide lasting amelioration of retinopathy with consistency, then the consequences seem even more alarming for the young individual with growth-onset diabetes. Obviously, the indications for such destructive procedures must be carefully weighed and the criteria for selection rigid.

Nevertheless, the majority of young diabetics, their families, and their physicians have found the price they must pay not too dear for the prevention of blindness. What additional palliation may accrue concerning other areas of vascular disease and other complications of diabetes remain to be determined in the years ahead. Perhaps there might even be a slight secondary gain of a biological nature in the sterility which results from hypophysectomy with the knowledge that growth-onset diabetes appears to be a dominant trait and particularly since the fertility rate appears high in the diabetic (*1*).

The surgeon and his associates are still faced with the dilemma of proper timing. It is now perfectly obvious that the major cause of failure, in addition to inadequate pituitary ablation, is the delay in withholding hypophysectomy until retinopathy is too far advanced. Indeed, our project suffered its most serious setback over 10 years ago when two patients who were almost totally blind were subjected to operation. These and a number of others subsequently lived out their existence with diabetes, blindness, and hypopituitarism. Thus, it is of paramount

Department of Neurosurgery, Lahey Clinic Foundation, Boston, Mass.

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importance that patients be selected early enough in the course of progressive retinopathy for operation to be beneficial. But to decide which patients will progress to inevitable blindness and which may be among the small group who seem to have a fortuitous arrest of the disease, as observed by Beetham (*2*) and others, remains a formidable task. Yet, if pituitary ablation is to remain a therapeutic tool, it must be employed earlier than it usually has in the past, and the ophthamologic criteria should be scrutinized with this in mind.

An editorial comment earlier this year suggested that "the encouraging results of pituitary ablation by either transfrontal or transsphenoidal route make it difficult to escape the conclusion that future controversy will center not so much on the value of pituitary ablation in diabetic retinopathy, as on the comparative merits of ablative approaches (*3*)." But should there really be such an argument about methodology? As the surgeon gains skill and experience with a particular technique, he comes closer to perfection, his results improve, and his complications are less common. The "comparative merits" as judged by results, morbidity, and mortality are also likely to be a reflection of experience with one technique or another—especially the experience of the entire team as its energies are focused upon a particular procedure, upon selection criteria, and postoperative management. Nowhere in any surgical endeavor has the team effort been of greater importance. But from the surgical aspects alone it would be folly to assume that the surgeon experienced in a cranial approach to the pituitary fossa could readily change to a transsphenoidal operation or implantation with the same measure of safety and success.

The advocates of instrumentation from below have likewise gained experience with their particular techniques and might find it difficult to pursue the route from above. Joplin et al. (*4*) have reported cerebrospinal fluid rhinorrhea in eight of 38 subjected to yttrium-90 implantations, all of these being followed by meningitis. The leak ceased spontaneously in four of the eight; in the remaining four, leakage continued until a tapered stainless steel screw was inserted by the same approach. There was only one death from meningitis and one other after severe hypoglycemia during recovery from meningitis. Forrest and coworkers (*5*) in their early attempts at radioactive implantation obtained inconsistent degrees of pituitary destruction with a high incidence of spinal fluid leakage and meningitis. Modifying their technique by utilizing the more popular screw type of implant for pituitary ablation in 42 patients and including indications for operation other than diabetic retinopathy, these authors had only three patients with rhinorrhea or meningitis or both. Others in recent years have been employing radiofrequency and cryosurgical probes

from below by stereotactic means and also proton beam radiation, apparently with increasing success (*6*, *7*, *8*, *9*).

Ray (*10*) however, met with an alarming morbidity and mortality following implantation of yttrium-90 as an alternate to surgical hypophysectomy in 22 patients with diabetes who, for one reason or another, were not considered suitable for craniotomy. The striking difference in complications, however, between this group and his excellent series of 56 patients (*11*, *12*) who underwent surgical hypophysectomy for progressive diabetic retinopathy was not the result of the advanced nature of their disease but, for the most part, of rhinorrhea, meningitis, and cranial nerve palsies.

Field, Sweet, et al. (*13*, *14*, *16*), have had no surgical deaths and no significant morbidity in their patients subjected to pituitary stalk section. Speakman et al. (*15*) have reported on 26 patients treated by pituitary stalk section (nine patients) and transsphenoidal hypophysectomy (17 patients) with one operative death in the former group and one cerebrospinal fluid leak and two cases of meningitis in the latter.

Adams, Daniel, and Prichard (*16*) have for years conducted the most comprehensive study of pituitary circulation and stalk section in man as well as other animals. In their most recent study, the pituitary glands of 21 patients who survived transection of the stalk for varying periods were examined. In every case the anterior lobe was abnormal. Infarcts or scars were present, usually of considerable size, but some parenchyma had always escaped destruction. This suggested that although pituitary stalk section will usually cause extensive infarction of the anterior lobe, this result will not be invariable. Our early clinical observations (*17*) suggested that pituitary stalk section alone was not as consistently effective in producing hypopituitarism as subtotal or total hypophysectomy. Bergland, Ray, and Torack (*18*) have indicated the anatomic pitfalls of the transsphenoidal, stereotactic type of procedures, and have emphasized the variations in the relationship of the internal carotid arteries, cavernous sinus, and surrounding bone to the hypophysis. Hardy (*19*), utilizing his elegant transsphenoidal microsurgical technique, appears to have the solution for all those who believe that they must operate through the nose. His procedure employs direct microscopic visualization of the gland and he has, thus far, had only one instance of cerebrospinal fluid leakage in over 30 diabetic patients.

Whether the controversy is a justifiable one or not, arguments are still being advanced by proponents of each procedure. References in the literature to the risk of cerebral damage by the cranial approach are numerous; yet, in our experience this risk is now virtually non-

existent. There is the argument that an approach from above may damage the optic nerves, but it is now evident that more optic nerves have been damaged by blind probing from below and by radiation extending beyond the confines of the gland. It is also a curious paradox that the incidence of lasting diabetes insipidus seems greater among patients who have had transsphenoidal operations, even in Hardy's group who have undergone selective anterior lobe resection. Thus far, at least, it seems easier to protect the pituitary stalk against traction and other damage by delicate visualization, dissection, and low incision, which can only be accomplished by a direct approach.

Strangely enough, many physicians and their patients are still reluctant and fearful to accept a relatively safe craniotomy, but readily agree to a procedure that is far more hazardous in some situations, often more painstaking, and usually more time consuming (a real concern for the severe diabetic under anesthesia). We have continued to utilize surgical hypophysectomy for these reasons and also because direct exposure appears to offer the best chance of adequate pituitary ablation with consistency in our experience.

In some of our earlier operations, section of the pituitary stalk alone and subtotal resection of the gland have since proved to be inadequate. From another important standpoint, it can also be said that we have not encountered a single instance of postoperative infection, rhinorrhea, or meningitis, despite the fact that on several occasions it has been necessary to open the sphenoid sinus from above to gain a clear anatomical exposure of the gland.

The disadvantages in the frontal approach to the pituitary gland are also those related to anatomical variation, one of the major variables being the position of the optic chiasm. In the most ideal situation, the exposed portion of the optic nerve is long, the chiasm placed well posteriorly, and the pituitary stalk can easily be seen from above without displacing the optic nerve. The situation is even more favorable if the chiasm has a relatively obtuse angle (fig. 1B). The least favorable presentation of the chiasm is in a forward position, the optic nerves appearing foreshortened, and the space between the anterior border of the chiasm and the tuberculum (sometimes having a long posterior extension) greatly foreshortened or nonexistent, the chiasm itself offering a barrier to the stalk and hypophysis (fig. 1C). Between these two extremes there are, of course, varying gradations, although in nine of 10 patients, entrance to the pituitary fossa anterior to the chiasm is adequate.

Another important variation deals with the depth of the chiasmatic cistern or, more properly, that portion of the cistern lying below the optic chiasm, between it and the diaphragma sellae. In some cases

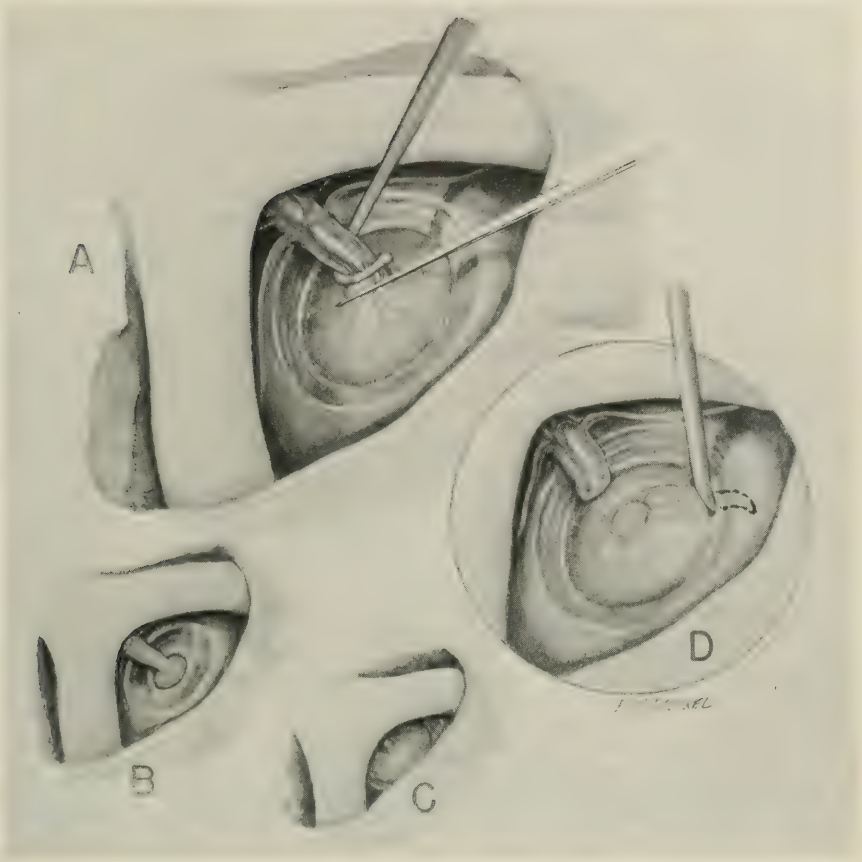

FIGURE 1.—*(A) Low incision of pituitary stalk after dissection with small, insulated nerve hook. (B) Favorable position of optic chiasm permits ready access to stalk and gland. (C) Anterior position of chiasm with limited space for dissection of stalk and gland. (D) Dissector beneath diaphragma sellae begins enucleation of gland.*

the cistern is very shallow, the superior surface of the gland almost seeming to bulge upward through a wide open sella. This allows for great accessibility and permits a good dissection of the gland beneath the diaphragma. In other instances, however, the cistern is deep, the gland is well below the optic chiasm almost buried within the sella, and the superior aperture is extremely small and limited.

Another important limiting factor, but perhaps less variable, is the width of the circular or coronal sinus—the large, round, venous channel lying in the periphery of the diaphragma connecting the cavernous sinsuses in crownlike fashion above the gland. Injury to this structure must be avoided to keep the field bloodless and allow for a complete dissection of the gland. A narrow sinus with a large dome of

gland presenting within its confines makes for a relatively easy dissection; the reverse is true when the sinus is wide and only a small portion of the gland is visible. Each of these adverse variations lends itself to one or another correctible maneuver, however.

Much of the success in proper exposure is dependent upon the anesthesiologist. Spinal drainage, however, is mandatory. Our practice is to carry out lumbar puncture under light pentothal narcosis with the patient sitting on the edge of the operating table supported by attendants. The back is relaxed in this position; lordosis disappears, and the lumbar puncture can be performed low at the fifth lumbar-first sacral level in the midline where rapid drainage is simple. At least 60 cubic centimeters of cerebrospinal fluid are removed and the needle then withdrawn. If, for any reason, a satisfactory puncture cannot be made, then 50 to 60 cubic centimeters of fluid are aspirated by cisternal puncture. The patient is then placed in the prone position, induction is continued with pentothal, and the trachea is intubated. Within a few minutes hyperventilation is begun along with the inhalation anesthesia. These techniques allow for a small frontal bone flap to be turned quickly and easily since the dura is relaxed. A single incision can be made in the frontal dura, and there is virtually no danger of trauma to the frontal lobe. The gentlest of retraction is required.

Most of these operations have been performed from the right side, but in those instances in which the left eye is hopelessly blind the approach has been made from the left. In any case, the olfactory tract on the side being operated on is divided, reasoning that it would never be functional after operation, and that its cauterization and division prevent annoying venous bleeding that can come from traction. The undersurface of the frontal lobe overlying the chiasm is carefully protected by Cottonoid pledgets; the chiasm is exposed, preserving as much arachnoid as possible over the optic nerves to avoid damage to small blood vessels. The pituitary stalk and gland are then visualized. Vision between the optic nerves can be improved slightly, if necessary, by rotating the head toward the operative side (fig. 2).

If the ideal or even favorable anatomical situation prevails, the stalk is delicately divided at the very surface of the gland after coagulating the portal vessels and loral arteries with lower current, using insulated instruments (fig. 1A). There is little or no traction on the stalk itself. With special, fine, curved, blunt dissectors, a global dissection is begun around the superior surface of the gland, freeing it from the overlying diaphragma and then sweeping around the gland beneath the coronal sinus anteriorly first and then posteriorly (fig. 1D). This allows for subsequent removal of the gland

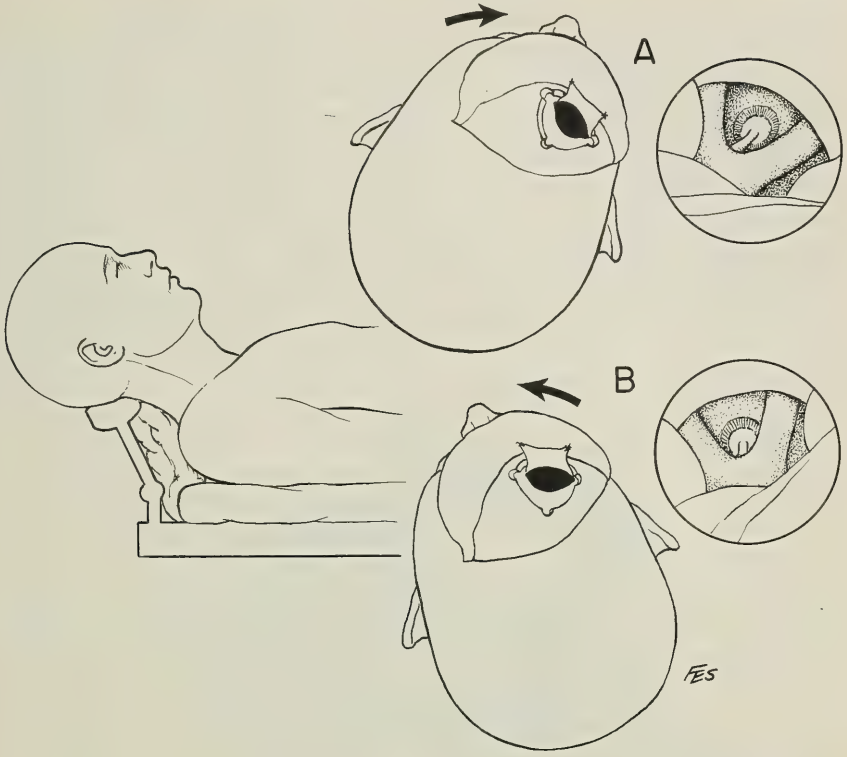

FIGURE 2.—*Diagram to show how rotation of head toward operative side (A) tends to "open" chiasm, while opposite rotation tends to obstruct view of pituitary (B).*

in two or three large fragments and then permits good visualization of the sella for removal of any retained gland, retracting the optic nerve slightly if this becomes necessary.

If the gland appears enclosed by an anteriorly placed chiasm, a posterior extension of tuberculum, or both, then the bony tuberculum is removed and the sphenoid sinus opened anteriorly, carefully preserving the mucosa. It is thus possible to strip the mucosa downward removing as much bone as necessary from the anterosuperior portion of the sella to convert the anatomy and again visualize the pituitary stalk and gland before proceeding. The gland enucleation can then be accomplished in the same way after dividing the stalk, and the gland may be removed from above or anteriorly, depending upon the size of the coronal sinus. If there is still any question about the possibility of a small, retained fragment of gland, the sella can be swabbed out with a formaldehyde solution, as recommended by Ray (*20*). In instances in which the sphenoid sinus has been opened, the mu-

cosa is stripped downward and the sinus then packed thoroughly with muscle and Surgicel (fig. 3). This type of packing is also occasionally necessary in the frontal sinus if it has been opened during the turning of the bone flap. The entire area is irrigated with a bacitracin solution of 50,000 units in 50 cubic centimeters of saline, but no antibiotics are given postoperatively. Replacement of the bone flap and closure of the wound are simple. The entire procedure take 1 to 1½ hours, and within the next hour the patient is awake.

Convulsive episodes have been observed in two patients postoperatively, so that Dilantin is now given after operation for 1 week. There

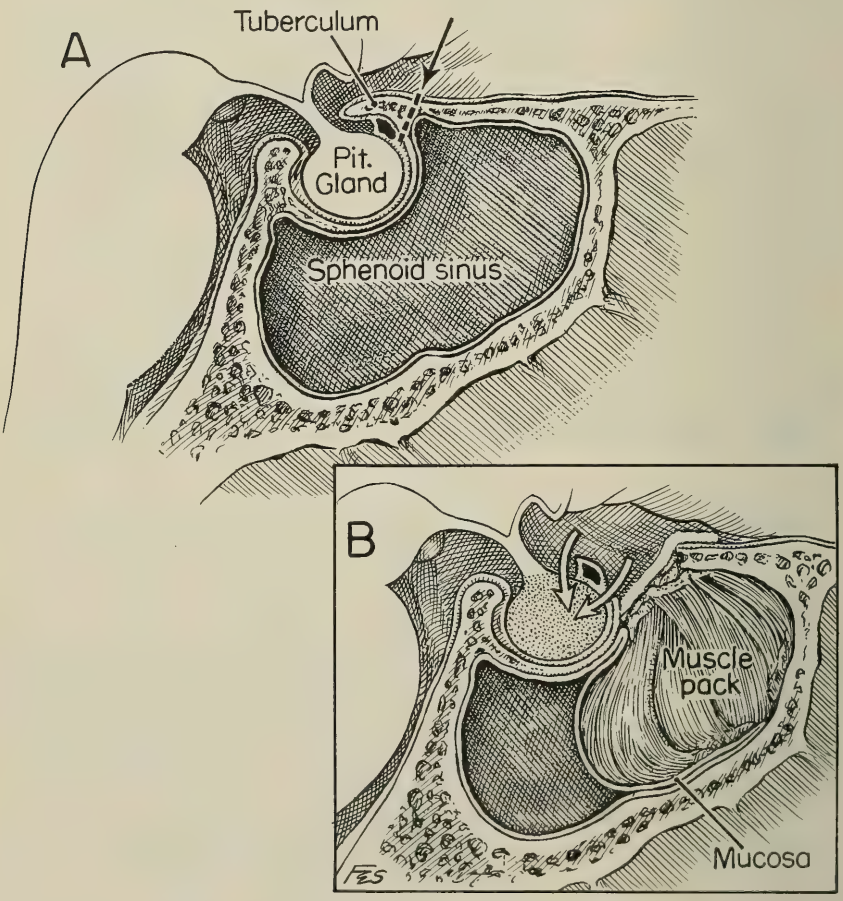

FIGURE 3.—(*A*) *Diagram to show posterior extension of bone from tuberculum and portion which must be removed. Approach to gland can then be above or below coronal sinus (shown in black).* (B) *Mucosa of sphenoid sinus is preserved and dissected away from opening, which is then packed with muscle after gland is removed.*

has been only one surgical death early in the series. Bleeding occurred from a small artery in the frontal pole during the retraction. This necessitated amputation of the frontal pole, which was accomplished with no difficulty, but severe cerebral edema developed subsequently, which proved difficult to control. She became comatose on the third postoperative day and died 3 weeks later. This is clearly an avoidable type of catastrophe if proper attention is given to all of the details of spinal drainage and anesthesia as previously enumerated.

Postoperative management also requires a well-organized team approach. Most of the patients have some symptoms of diabetes insipidus during the first week after hypophysectomy. Pitressin is usually not given during the first 3 to 4 days unless the diuresis should be massive. However, it rarely exceeds 5,000 cubic centimeters in a 24-hour period, and we have found a mild degree of dehydration favorable in this period. Dexamethasone, likewise, is not administered unless there is some concern about cerebral edema; its use has been necessary in only a few patients. From the standpoint of control of the diabetes it has seemed better to administer cortisone, 200 milligrams daily during the first 3 days, then to begin gradual reduction of the steroid thereafter. Problems concerned with hypoglycemia, reduction of the insulin dosage, salt depletion, and postural hypotension are not usually evident before the end of the first week. The later problem of adrenal insufficiency, however, is a far more serious one and remains of real concern to all physicians who treat these patients.

SUMMARY

Different methods of pituitary ablation in the patient with diabetes become more successful as the team involved and the surgeon gain experience with one procedure or another. As transsphenoidal techniques have improved, surgical hypophysectomy has also become relatively safe and effective. The obstacles imposed by anatomical variations surrounding the pituitary gland have largely been overcome. While criteria for selection must remain rigid and the consequence of hypopituitarism and adrenal insufficiency are serious problems to impose upon the diabetic patient, some attempt should be made to consider patients for this type of therapy at an earlier stage of progressive retinopathy.

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CHAPTER 19

Radiofrequency Pituitary Coagulation for Angiopathic Diabetic Retinopathy [1]

RICHARD A. FIELD, M.D.
THOMAS BEHRENDT, M.D.
NICHOLAS T. ZERVAS, M.D.
PHILIP D. GORDY, M.D.
THOMAS D. DUANE, M.D.

INTRODUCTION

The qualified acceptance of pituitary ablation as a beneficial maneuver in ameliorating the prognosis of hemorrhagic diabetic retinopathy (*1*) has led to a search for methods of pituitary destruction which entail minimal stress and risk while providing certainty of immediate and substantial endocrine suppression. This report covers the experience employing the transsphenoidal stereotaxic technique and the production of multiple radiofrequency thermal lesions in 42 patients over a 2-year period. The features of the clinical course with this technique will be emphasized. Details of the technique and the anatomic considerations involved are covered in a companion paper (*2*).

METHODS

All candidates were ophthalmologically examined by T.B., but classification and characterization of the retinopathy were based upon interpretation of color retinal photographs and fluorescein studies. Whenever possible, fluorescein ciné-retinography was also employed.

Preoperative medical evaluation was carried out by R.A.F. Laboratory documentation of thyroid, adrenal and gonadotropic function was carried out by routine clinical methods. Electrocardiographic and radiographic studies were performed. Postoperative care was supervised by R.A.F. In all cases, except a few where patients came

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[1] See appendix C for raw data on individual patients.

From the Departments of Medicine (Division of Endocrinology and Metabolic Diseases), Ophthalmology and Neurosurgery, Jefferson Medical College of Philadelphia, Philadelphia, Pa.

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from distant locations, decision to recommend operation was based on two examinations at least 6 weeks apart.

Postoperative endocrine appraisal was derived from estimation of thyroid function as documented by PBI, radioactive I^{131} uptake and T_3 resin binding capacity and the occurrence of amenorrhea in females.

All operative procedures were performed by either N.T.Z. or P.D.G.

PATIENTS

The criteria for selection were those previously published except that greater leniency was allowed in regard to renal function and three patients had BUN levels in the 25 to 30 range (*1*).

The preponderance of males (55 percent) was less than in the stalk section series (79 percent) of Field *et al.* (*3*). The average age of 36.6 years was slightly older than the 34.5 years; the duration of diabetes was 19.6 years as compared to 19.9 years and the average duration of recognized retinopathy was 3.0 years as opposed to 2.3 years. As in the craniotomy series, where 74 percent of patients were blind in one eye, patients already blind in one eye predominated with 60 percent so afflicted. The left eye was blind in 14 cases and the right in 11. Again, as in the stalk section experience, the left preponderance was not statistically significant. Figure 1 summarizes the characteristics of the group by year of operation and as a whole.

The O'Hare Classifications [1] of the 59 sighted eyes were:

	Number	Percent		Number	Percent
N_0	0	0	F_2	17	29
N_1	17	29	H_0	37	63
N_2	42	71	H_1	22	37
F_0	30	51	H_2	0	0
F_1	12	20			

Therefore, the stage of retinopathy of the sighted eyes in this series appears to have been earlier than those in the stalk-section series and fewer regressions should occur as time passes.

It is noteworthy that two patients in this group had had attempts at production of hypopituitarism by other methods, one by proton-beam irradiation and the other by means of hypophyseal stalk-section. Both showed intact pituitary function and had not experienced an arrest of retinopathy. Following pituitary coagulation, both patients were judged to have had suppresson of pituitary function and a discernible

[1] O'Hare classification, p. XXI.

RADIOFREQUENCY
PITUITARY COAGULATION FOR ANGIOPATHIC DIABETIC RETINOPATHY
PATIENTS SELECTED BEFORE AUG. 15., 1968

	1967 - 68	1966 - 67	TOTAL
PATIENTS	25	17	42
SEX	13M	10M	23M (55%)
	12F	7F	19F (45%)
AVERAGE AGE	38.0	34.6	36.6 (19 - 62)
DURATION OF DIABETES	20	19	19.6 (1 - 35)
DURATION OF RETINOPATHY	3.3	2.5	3.0 (1 - 6)
PATIENTS BLIND IN ONE EYE	14 (56%)	11 (65%)	25 (60%)
	8 OS 6 OD	6 OS 5 OD	14 OS 11 OD

POST - OP DEATHS	0
SUBSEQUENT DEATHS	2 (5%)
UREMIA	1
VIRAL MYOCARDITIS	1

FIGURE 1.—*Characteristics of the patient population.*

objective, beneficial influence on the angiopathic component of the retinopathy.

PREOPERATIVE MANAGEMENT

Fortification of corticosteroid reserve was provided by a 50-milligram dose of hydrocortisone the night before operation, 75 milligrams given intramuscularly at the time of induction of general anesthesia and 100 milligrams intravenously in 1,000 milliliters of 2.5 percent glucose and 0.45 percent saline during the procedure. One-half of the patients' usual dose of intermediate-acting insulin was administered just before anesthesia induction. Body weight and hematocrit were determined as a baseline for guidance of post-operatve fluid and electrolyte management. Nose and throat culture were also included in the preoperative routine.

In the majority of cases, prophylactic administration of chloramphenicol and erythromycin was carried out; however, this practice has been recently abandoned.

POSTOPERATIVE MANAGEMENT

On arrival in the recovery room, a blood glucose determination was obtained and an appropriate dose of regular crystalline insulin prescribed. Patients regained full consciousness within 3 hours after termination of anesthesia. In no case did clinical examination of ocular movement and confrontation visual fields in the recovery room or thereafter reveal any evidence of damage to cranial nerves II, III, IV, or VI. In four early cases, there was evidence of unilateral paresis of the facial musculature which was determined to be the result of pressure on the course of cranial nerve VII by the fixation plug of the stereotaxic ring placed in the pinna and external canal of the corresponding ear. In one case, although there has been considerable reversal, an insignificant degree of residual paresis of facial muscles was still detected 1 year postop. In the other three cases, no detectable paresis was evident 3 months after the procedure. The fixation plug was modified and no facial paresis has been noted in the last 20 cases.

With rare exceptions, patients were able to take small amounts of oral fluids the afternoon of the procedure and a meal of soft solids by evening. Catheterization has not been necessary, and patients were allowed to stand to void or to walk with assistance to the lavatory during the evening of the day of operation. Regular insulin was administered every 4 hours after the first voiding, using the results of the urine testing for glucose and acetone as a guide to dosage.

One-half the patient's preoperative intermediate-acting insulin dose was continued on a daily-before-breakfast schedule on the first postoperative and subsequent days. The full preoperative diet was resumed by the third postop day, and supplemental insulin administration restricted to a before meal dose according to the results of urine testing.

Discomfort as the result of the irritation of the nasal pack was the principle source of postop complaint and was alleviated by removal of the pack in 8 to 12 hours after the procedure had been completed. In a few instances, midfrontal headache constituted a source of mild to moderate continuing discomfort for as long as a week. The cause of this problem appeared to be irritation or the formation of a clot in the sphenoid sinus. Partial relief of symptoms was obtained by neosynephrin nose drops and salicylate analgesia. Only a few patients had one degree or less temperature elevation during the first 48 hours.

Less than half of the cases demonstrated definite diabetes insipidus which could be confirmed by the simultaneous production of hypo-osmolar urine in the face of hyper-osmolar plasma; however, there was, in most cases, a substantial increase of daily intake and output to the 5,000 to 7,000 milliliter range, associated with 4 to 6-pound, evening-to-morning weight variation, at some time during the first week.

The administration of vasopressin in oil was required, usually in the first 72 hours postop, in less than 25 percent of the cases. Only one patient has continued to require injections of vasopressin more than 3 months postop.

The amount of oral fluid intake was regulated by the patients themselves according to their subjective sensations of thirst, and they were advised not to force fluids beyond the amount required to satisfy their thirst. The appearance of an antidiuretic phase was not detected with certainty in any patient, and in no instance was a postoperative serum sodium below 130 mEq/L found on serial determinations.

Mild, asymptomatic hypokalemia ($K<4.1$ mEq/L) appeared at or after the fifth postop day in approximately 50 percent of the cases and was easily corrected by the administration of oral potassium supplements.

A transient rise of BUN to the 35 to 70 milligrams per 100 milliliter range was noted in those patients in whom borderline or slightly elevated preoperative BUN had been found. This finding was interpreted as being the result of the drop in glomerular filtration rate which follows successful hypophysectomy (*4*).

Gradual, stepwise reductions of hydrocortisone dosage from 75 milligrams per day were carried out starting 48 hours postop by decrements of 15 milligrams per day, so that a maintenance level of 20 milligrams before breakfast and 10 milligrams before supper was achieved by the sixth postop day. Thyroid function tests and ophthalmologic reevalaution were carried out between the 11th and 14th days after operation. L-thyroxine, 0.2 milligram per day in all patients, and depotestosterone, 200 milligrams every 14 days in male patients, were started upon the completion of testing.

Discharge from hospital occurred from the 12th to 14th postop day, and the average total hospitalization time was 20 days. Final insulin dosage adjustment was deferred until the patients had resumed full activity approximately 3 weeks after discharge. In most cases, the females had replacement estrogen added to their programs by their local physicians. There was a greater than 25 percent reduction in insulin requirement by the time of discharge and further subsequent reduction in many cases. Libido and potentia have been maintained by the males who possessed them preoperatively.

FOLLOWUP

Patients were requested to note on a report form the results of daily weights, urine tests, along with occurrence of insulin hypoglycemia, changes in subjective visual acuity, occurrence of diabetes insipidus

or alterations in the treatment program. More than three-quarters of the patients have kept these forms posted faithfully and have forwarded them on a biweekly basis. Whenever possible, patients return for fundus photography, medical evaluation and ophthalmologic examination at 3, 6, and 12 months postop. All are provided with, and instructed to carry, a special card identifying them as hypophysectomized and advising massive corticosteroid reinforcement in the event of emergency.

MORBIDITY AND SUBSEQUENT MORTALITY

In the earlier application of the radiofrequency pituitary coagulation technique in the treatment of 84 patients with cancer, Zervas and Gordy (*5*) reported that one patient died postoperatively of meningitis and four of seven cases who had cerebrospinal fluid rhinorrhea developed meningitis. As detailed in the companion paper (*2*), the alteration of technique allowing a single midline puncture of the sella and the adoption of the practice of occluding the puncture tract with either a muscle tampon or silicone plug has all but eliminated the occurrence of meningitis and rhinorrhea. In this series, one patient developed definite cerebrospinal fiuid rhinnorhea during jet travel and returned for successful replacement of a muscle tampon; a second patient complained of postnasal drainage and, although definite rhinorrhea could not be established, the silicone plug appeared to be improperly positioned on X-ray and was replaced. There have been no postoperative deaths or meningitis.

One of the two subsequent deaths was due to inexorable advance of the preexistent uremia and occurred 10 months postoperatively. The other death occurred 9 months postop following a fulminant respiratory illness and was attributed to a viral myocarditis by the examining pathologist.

RESULTS

Endocrine: In four of the 42 cases, there is insufficient postoperative data for evaluation of endocrine status. In the 38 remaining cases, there was a drop in PBI below 4.0mcg. per 100 ml. and a reduction in radioiodine uptake below 15 percent in all instances.

Of the 19 females, four were postmenopausal at the time of surgery; and, of the 15 menstruating females, none has continued menses beyond a single episode of vaginal bleeding immediately postop. Neither breast enlargement or galactorrhea have occurred in any of the fe-

males and none has become pregnant. None of the male patients have sired children.

As previously mentioned, a 25 percent or greater fall in insulin requirement has been experienced in all cases. There have been no instances of crises of adrenocortical insufficiency or of serious hypoglycemic episodes.

Ophthalmologic: Failures are defined as cases in which the existing preoperative macular vision had been lost within 6 months after the procedure. This event occurred in five cases, four from recurrent vitreous hemorrhaging and one from retinal detachment. Stabilization or improvement has occurred in the remaining 37 instances.

In the case of 50 sighted eyes in which there has been sufficient observation for comparison, the following changes in visual acuity have occurred:

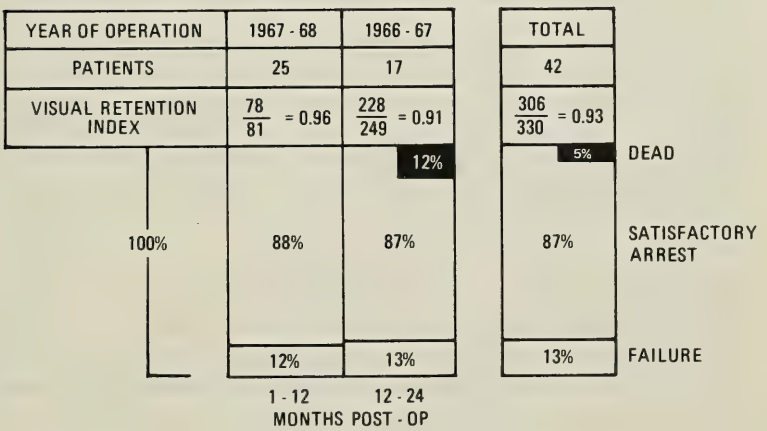
		Percent
Improved	16	80
Unchanged	24	
Worse	10	20

Three cases (20%) from the group of 15 survivors more than 1 year postop have reached a stage of "involuted retinopathy" as defined by Beetham (*6*).

RADIOFREQUENCY

PITUITARY COAGULATION FOR ANGIOPATHIC DIABETIC RETINOPATHY

EXPERIENCE ON PATIENTS SELECTED BEFORE AUG. 15, 1968



NB: 1 PATIENT HAD UNDERGONE PREVIOUS PHOTOCOAGULATION
1 PATIENT HAD UNDERGONE PROTON - BEAM PITUITARY IRRADIATION
1 PATIENT HAD UNDERGONE HYPOPHYSEAL STALK SECTION
2 (4.0%) REQUIRED REPLACEMENT OF PLUG

FIGURE 2.—*Summary of 2-year follow-up of the 42 cases.*

DISCUSSION

Transsphenoidal radiofrequency pituitary coagulation has proved to be a useful method of pituitary ablation in the treatment of angiopathic retinopathy. The mortality and morbidity have been reduced to nonexistent or inconsequential levels with the modifications of single sellar puncture and sealing of the probe tract with a silicone plug. As judged by changes in thyroid function and menstrual activity in females, a significant degree of functional pituitary suppression was achieved. From 2 years of observation of 42 cases, it appears the same character of changes in retinal angiopathy are produced, and an equivalent improvement in visual prognosis can be achieved as with surgical methods.

In comparison with procedures requiring craniotomy, the amount of discomfort, stress and of disturbance of fluid and electrolyte balance proved to be drastically reduced. The requirement for prolonged immobilization, catheterization, intravenous therapy, special nurses and prolonged wound healing was virtually eliminated. There appeared to be a considerably lower frequency of occurrence of significant diabetes insipidus, and no instances of hyponatremia due to ADH dependent antidiuresis were encountered. The relative benignity of the procedure suggests that it could be safely extended to the azotemic and less medically qualified patients. The experience in 11 such patients with azotemia or other serious medical limitations previously reported (*7*) is in accord with this proposition.

The advantages of the radiofrequency methodology over pituitary radiation proved to be its immediacy of hormonal effect and certainty of producing it as well as freedom of evidence of injury to structures adjacent to the pituitary. The difficulties with cerebrospinal fluid rhinorrhea associated with radionecrosis of the sellar floor following transsphenoidal radiation implantation were not encountered. The security of freedom from injury to adjacent structures enjoyed when employing heat as the modality of tissue destruction allowed the use of general anesthesia. This appears to be the only advantage over the cryodestruction technique.

Although the mechanism of the beneficial effect of pituitary ablation is unknown, it is an attractive hypothesis that the retinal changes are the result of the removal of a pituitary or hypothalamic humoral factor. Circumstantial and direct evidence indicate that neither gonadotropins nor somatotropin appear to be the culpable factors (*8*). The versatility and flexibility of the stereotaxic radiofrequency technique provides the possibility of partial or selective pituitary destruction

and promises to be a suitable method for exploration of such investigative trials.

SUMMARY

(1) Forty-two cases of stereotaxic radiofrequency pituitary coagulation for angiopathic diabetic retinopathy have been followed for 2 years. The group was 55 percent male, 45 percent female and had attained an average age of 36.6 years after an average duration of 19.6 years of diabetes and 3 years' duration of retinopathy. Sixty percent were already blind in one eye at the time of operation.

(2) There was no operative mortality or meningitis, and two easily remediable cerebrospinal fluid leaks occurred. The low frequency of complications was attributed to the entry into the pituitary by way of a single puncture of the sella and closing the tract with a silicone plug.

(3) The postoperative course of the patients was remarkably benign, medically uncomplicated and easily managed. There was a minimum of patient discomfort and few instances of significant diabetes insipidus.

(4) As judged by changes in thyroid function, menstrual activity and reduction of insulin requirement, the procedure achieved a substantial degree of endocrine ablation.

(5) The results of ophthalmologic evaluations indicated improvement in prognosis for retention of macular vision equivalent to that achieved by other methods of pituitary destruction for a similar postoperative interval.

(6) The experience suggested, by reason of its certainty, safety and benignity, that it can be used in patients with moderately advanced renal disease or who are otherwise medically unfit for elective craniotomy. The versatility provided allows consideration of the procedure in future investigative trials of controlled selective and partial pituitary suppression.

Acknowledgment

The contributions of Drs. John F. Aloia, William E. Caskey, Mr. Jay Skyler, Mr. Kenneth Pickren, Mrs. Katherine Dougherty and Miss Patricia Cephas to various phases of this work are gratefully acknowledged.

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CHAPTER 20

Hypophyseal Stalk Section for Angiopathic Diabetic Retinopathy

RICHARD A. FIELD, M.D.
J. WALLACE McMEEL, M.D.
WILLIAM H. SWEET, M.D., D.Sc.
CHARLES L. SCHEPENS, M.D.

INTRODUCTION

In 1961 the first three patients of this series were reported (*1*), and interim reports have followed (*2*). This paper summarizes and analyzes a comprehensive survey made as of August 1968 of experiences gained from 120 patients who underwent hypophyseal stalk section beginning in 1959 until November, 1966. The criteria of selection of patients and the details of surgical technique have been well established and previously published. The objectives of this report are to attempt to evaluate the clinical usefulness of pituitary ablation and to discover, if possible, clues which provide understanding of the mechanisms and pathogenesis of retinopathy.

PATIENTS

In order to make valid comparisons with other series and to define the effects of the criteria of selection employed, the characteristics of the population have been tabulated (fig. 1). Certain features of the group bear emphasis and may be of importance.

Sex

The overwhelming preponderance of males (79 percent) has been presumed to be due to the threatening impact of impending blindness on the socioeconomic status of the family provider. Understandably, this would lead to stronger motivation to seek remedy and accept elective operative intervention in hopes of prolonging gainful activity. Nevertheless, the wide disparity, consistently present in each year's

From the Departments of Medicine, Ophthalmology and Neurosurgery, Harvard Medical School, Boston, Mass. and the Departments of Medicine (Diabetes Unit) and Neurosurgery, Massachusetts General Hospital, Boston, Mass. and the Retina Service, Massachusetts Eye and Ear Infirmary, Boston, Mass.
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HYPOPHYSEAL STALK SECTION FOR ANGIOPATHIC DIABETIC RETINOPATHY

PATIENTS SELECTED BEFORE NOV. 1., 1966

	1966	1965	1964	1963	1962	1959 - 61	TOTAL
PATIENTS	10	22	29	18	25	16	120
SEX	7M	15M	19M	12M	18M	12M	83M (79%)
	3F	7F	10F	6F	7F	4F	37F (21%)
AVERAGE AGE	31.3	34.5	35.3	31.3	35.2	37.6	34.5 (18 - 58)
DURATION OF DIABETES	18.0	19.2	20.2	23.3	19.0	18.8	19.9 (1 - 37)
DURATION OF RETINOPATHY	2.2	2.3	2.6	1.9	2.4	2.1	2.3 (1 - 7)
PATIENTS BLIND IN ONE EYE	5 (50%)	15 (68%)	23 (79%)	13 (72%)	21 (84%)	12 (75%)	89 (74%)
	3 OS 2 OD	6 OS 9 OD	13 OS 10 OD	8 OS 5 OD	13 OS 8 OD	6 OS 6 OD	49 OS 40 OD
	2	3	4	5	6	7 - 9	

YEARS POST - OP

FIGURE 1.—*Characteristics of the patient populations in regard to sex, age, duration of diabetes and retinopathy and blindness in one eye.*

grouping, prompts a reconsideration of the possibility that the sex frequency disparity reflects an inherent difference between the sexes in either the frequency of occurrence of hemorrhagic retinopathy or in the as yet unknown factors of pathogenesis which might contribute a greater risk of blindness in the male diabetic population.

Age and duration of diabetes

Although the span of age ranges from 18 to 58 and that of duration from 1 to 37 years, the consistency of the averages of 35 and 20 years respectively is impressive. All but two of the group were insulin dependent and ketogenic and had experienced one or more episodes of significant ketoacidosis in the early years of their disease.

Duration of retinopathy

There is an evident sharp contrast of the relatively short period, 2.3 years, between detected onset of retinopathy and progression to a sight threatening stage in this group and the relatively indolent tempo of

progression in the nonangiopathic forms of retinopathy such as the primarily exudative variety most frequently seen in the adult-onset diabetic population.

Unilateral blindness

As discusssed in more detail in Dr. McMeel's paper,[1] intervention was reserved until serial examination indicated relentless progression of angiopathy and an element of desperation was evident. This is reflected by the circumstances of 74 percent of the patients being blind (visual acuity $< 20/200$) in one eye at the time of operation. This consideration gives an index of the stage of advancement of the process in this group and provides a point of reference for prediction of prognosis for the still sighted eye had the patients been left untreated.

It is of some interest that, early in this experience, a preponderance of the left eye being the blind one when only one sighted eye remained was noted; however, while this preponderance tended to persist with later cases, the overall difference of preop blindness between left and right is not statistically significant at the 5 percent level. On the other hand, the fact that the left eye preponderance was present in five out of the six groups would be expected only 12 percent of the times had equal probability for each of the groupings been present. Therefore, while not certain of the validity of greater liability of the left eye to earlier blindness, it appears reasonable to continue to maintain a level of suspicion that relative perfusion pressure of a given eye may play a role in the hemorrhagic events, based on the more direct communication of the left ophthalmic artery with the aortic arch and the observation that intravenously injected fluorescein appears first in the left eye twice as frequently as it does in the right.

Twenty-one of the 151 sighted eyes were O'Hare class N_1 while 130 were N_2 (86 percent).[2] Thirty-one of the 151 sighted eyes were O'Hare class F_1 while 120 were F_2 (79 percent). Details of the ophthalmologic characteristics of the patients are available in Dr. McMeel's paper.[1]

Methods of evaluation and classification of results

Until November 1966, all patients were medically evaluated and followed by Dr. Field and were examined ophthalmologically by Dr. McMeel and his colleagues of the Retina Service of the Massachusetts Eye and Ear Infirmary. In a handful of cases, it was necessary to rely

[1] J. W. McMeel: Hypophyseal Stalk Section as Treatment for Diabetic Retinopathy; Ocular Aspects, ch. 26.

[2] See O'Hare Classification, page XXI.

on reports from other internists and ophthalmologists attending patients from distant locations. More than 75 percent of all the patients have continued to report by mail on a biweekly basis using a standardized report form concerning their medical and visual status. After November 1966, 18 of the patients more than 3 years postop found it more convenient to be followed in Philadelphia when Dr. Field relocated. Their subsequent ophthalmologic examinations have been carried out by Drs. Behrendt and Duane of the Department of Ophthalmology of Jefferson Medical College. The Jefferson methodology of ophthalmologic examination differed from that described by Dr. McMeel in that indirect ophthalmoscopy was not performed and evaluation of the fundi was based on color and fluorescein still and ciné photography.

The adequacy of followup was best in the 5-year and 7- to 9-year postop groups with a recent examination available in 89 percent and 87 percent respectively. Followup adequacy was poorest in the 2-year postop group where recent examination was available in 80 percent of the cases.

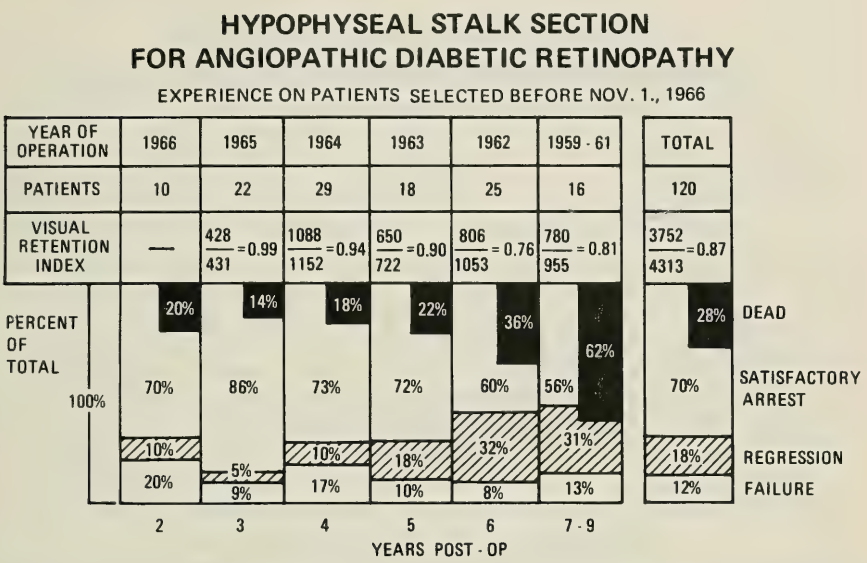
RESULTS

Figure 2 summarizes the findings by groups and *in toto*. The term "failure" has been applied to those cases in which, although some of the early changes in regard to increased vitreous translucency and venous dilatation may have been observed, recrudescence of vitreous hemorrhaging ocurred relatively soon postop and the patient at 6 months had vision worse than preop.

The term "regression" has been assigned to those cases in which gratifying changes occurred over at least 6 months but subsequently vision deteriorated and was worse at the time of survey than it had been preop. A compilation of the causes of failures and regressions indicated that only 30 percent were due to recurrent vitreous hemorrhaging while 67 percent were the result of nonrhegmatogenous retinal detachment and extension of flat gliosis over the macula. Regressions appeared to continue at a seemingly steady rate throughout the period of observation and the median time between operation and regression was approximately 3 years.

Satisfactory arrest was considered to have occurred when visual acuity remained stable or improved and the O'Hare class either remained unchanged or improved. In 49 (32 percent) of the 151 sighted eyes at risk, there was an objective improvement in the O'Hare N rating; 23 (15 percent) improved in regard to H rating and 21 (14 percent) improved in regard to F rating.

Comment must be made on the employment of photocoagulation



NB: 14. PATIENTS HAD 28 INSTANCES OF SUBSEQUENT PHOTOCOAGULATION THERAPY
2 PATIENTS HAD SUBSEQUENT CATARACT EXTRACTION
3 PATIENTS HAD SUBSEQUENT RESUMPTION OF PITUITARY FUNCTION

FIGURE 2.—*Summary of 2 to 9 years follow-up of the 120 cases.*

in 14 patients in 28 instances. This procedure was carried out whenever an accessible source of recurrent hemorrhage could be identified or when the ophthalmologist felt an accessible residual neovascular formation threatened further hemorrhage. Two patients required subsequent cataract extraction because of increasing lenticular opacity.

Mortality

There were three operation-connected deaths, one from myocardial infarction and two from thrombophlebitis of the leg veins and massive pulmonary embolism.

Thirty-three of the 120 patients (25 males, 6 females) have subsequently died. Figure 3 tabulates the causes of death and the average duration of survival of the deceased patients. Except for the 2-year postop group, which is smallest in number and accounted for two of the deaths, there was a steady death rate with time, and in only one case, that of insulin hypoglycemia, could the death be said to have been dependent on the patient's having pituitary insufficiency. One death, that caused by an automobile accident, was unrelated to either diabetes or hypopituitarism. Myocardial infarction accounted for more than half of the deaths. Cerebrovascular accidents and progressive

HYPOPHYSEAL STALK SECTION FOR ANGIOPATHIC DIABETIC RETINOPATHY

PATIENTS SELECTED BEFORE NOV. 1., 1966

MORTALITY

CAUSES OF DEATH:	(33 of 120)	%
CORONARY ARTERY DISEASE		55
CEREBROVASCULAR ACCIDENT		15
UREMIA		15
PULMONARY EMBOLISM		6
INSULIN HYPOGLYCEMIA		3
STAPHYLOCOCCAL PNEUMONIA		3
AUTOMOBILE ACCIDENT		3
		100
POST - OPERATIVE DEATHS	3	(2.5%)

AVERAGE SURVIVAL OF SUBSEQUENT DEATHS

YEARS POST - OP	NUMBER DEAD	YEARS
7 - 9	10 (62%)	4.5
6	9 (36%)	2.7
5	4 (22%)	2.7
4	5 (18%)	2.2
3	3 (14%)	2.0
2	2 (20%)	1.0

FIGURE 3.—*Mortality experience.*

renal failure constituted another 30 percent. Thus, some form of diabetic vascular disease was the cause of death in 85 percent of the instances. The deaths were divided between the sexes in the same proportion as the sex distribution of the group as a whole.

Influence of Age and Sex

Figure 4 represents an analysis of the ophthalmologic results of all patients more than 3 years postop by age and sex. The success rate in those under 40 at the time of operation was 80.6 percent while that in the over 40 group was only 46.9 percent. The difference between the two groups is statistically highly significant ($P = < 0.001$). This situation obtains from a fourfold greater failure rate and a twofold greater regression rate in the older age group.

When the experience was examined for a difference in results related to sex, it was found that none existed and there was an equal distribu-

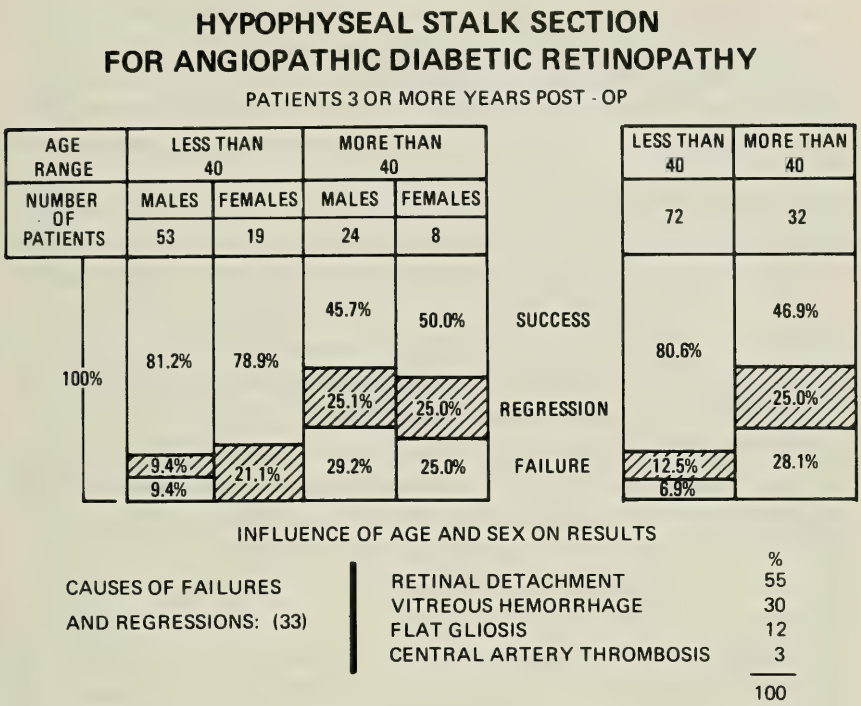


FIGURE 4.—*Comparison of results in patients under and over the age of 40 and causes of failures and regressions.*

tion of males and females in each of the categories—success, regression, and failure—in both the younger and older patients.

The limited prognosis for life and continuing activity of patients with advanced proliferative retinopathy has been emphasized and documented by Patz and his associates (*3*). It does not appear from a comparison of their observations and the mortality experience in this group that a significant acceleration of death rate, over and above that contributed by the low operative mortality of 2.5 percent, has been associated with induced hypopituitarism.

Visual Retention Index and Involutionary Phase

As defined, the visual retention index is an expression of the eye-months of retained macular vision divided by the number of eye-months at risk. Thus, according to our observations, there is an approximately three out of four probability that a stalk-sectioned patient will have retained equivalent or better macular vision 7 to 9 years postoperatively, provided he survives; and there appears to be

an only slightly better than one out of three chances that he will. Corresponding probabilities for the 6-year postoperative interval are about the same for retained macular vision but a two out of three probability of survival. At 3 years postop, the situation was much more encouraging with a better than four out of five chances of retained vision and six out of seven chances of survival.

The difficulty of assessing the apparent enhancement of prognosis for vision brought about by the intervention in an uncontrolled experience such as this series is in part lessened by the frequency of occurrence of an "involutional phase" of the active proliferative retinopathy. Drs. Behrendt and Duane have been impressed by the number of instances in which not only cessation of new vessel growth and ingrowth of fibrotic tissue occurred in the 18 cases of this series, which they have had the opportunity to examine, but in which actual involution with only dense shrunken avascular empty fibrotic strands could be detected (*4*). Of the 18 cases of this series they have examined, all of whom were more than 2 years postop, they judged 16 or 89 percent were in such an involutional phase. In their own experience, they could find only one case where such involution had occurred spontaneously. Although it is probable that the patients who wished to be followed in Philadelphia have had more favorable results, those with involuted retinopathy constituted 13.4 percent of the total group. Beetham (*5*), in 1963, reported only eight spontaneous instances out of 351 patients (2.3 percent) who might be classified as having reached such an involuted phase. Thus, at an absolute minimum, since some of the patients not followed in Philadelphia can be predicted to have reached this phase of proliferative retinopathy, the experience in the total group is at least fivefold and nearly sixfold better than that observed to have occurred spontaneously.

Correlations of Ocular Results with Pituitary Function

In the first 13 cases of this series, extensive testing of the several spheres of pituitary function documented nearly total cessation of function following hypophyseal stalk section. Thereafter, because of the difficulties involved—prolongation of hospitalization and the expenses involved—assessment of endocrine results were based on alterations of thyroid function, occurrence of amenorrhea in the females and reduction of insulin requirement.

Three patients were observed in whom, after a period of documented hypopituitarism, there was obvious resumption of pituitary function.

In two of these cases, there had been a temporarily related exacerbation of hemorrhagic events and neovascular activity. In one case extirpative hypophysectomy was performed, and a subsequent clinical remission of retinopathy ensued. In the other case associated with exacerbation of retinopathy, reoperation was declined, and blindness ensued within a year. In the third case, a 20-year-old female, there was a dramatic involution of hemorrhagic activity and amenorrhea for approximately 1 year. No exacerbation of retinopathic activity was noted after resumption of menses or during a subsequent pregnancy which resulted in a viable, normal child.

In four cases in which recrudescence of hemorrhagic activity occurred after more than 2 years of gratifying remission, extensive, exhaustive endocrine investigation failed to define any detectable resumption of pituitary function in regard to gonatotropins, TSH or ACTH. Low and variable levels of somatotropin were present.

In order to probe the role of somatotropin on the ocular changes following hypophyseal stalk section, 18 patients were tested for somatotropin responses to insulin-induced hypoglycemia before and several months after surgery (*6*). It was found that somatotropin responses were frequently abnormal in patients with diabetic retinopathy and that angiopathic eye changes, even when beneficially influenced, occurred independently of somatotropin changes.

Correlation of Results with Renal Pathology

All patients in this series had preoperative open renal biopsies. In an attempt to correlate the ophthalmic results with the elements of renal pathology, 50 cases, in whom more than 2 years of clinical progress had been documented, were studied. Twenty-five cases had experienced poor eye results and 25 cases were chosen where there had been dramatic ocular improvement. Thirty-three of the biopsies were adequate for the determination of the extent of change of 26 precisely defined, morphologic histopathologic parameters. Each parameter was graded by two observers who were unaware of the clinical courses the biopsy donors had experienced. Good correlation with clinical results was obtained only with hyaline thickening of prehilar and hilar changes of the glomerular arterioles (*7*). In 17, where advanced pathologic changes in this component of diabetic renal disease were present, 12 (71 percent) had experienced poor clinical results in regard to their retinopathy; in 16 cases, in which the arteriolar lesion was minimal, 14 (87 percent) patients had experienced a gratifying ocular course.

Thus, in five cases where poor clinical results were predicted because of glomerular arteriolar lesions, good ophthalmologic results occurred, while in two cases in which renal pathology predicted a good result, a poor clinical result was actually obtained ($X^2=9.13$, $P=<0.01$).

DISCUSSION

Diabetes mellitus is a highly variable clinical disease whose fundamental causation, despite a prodigious amount of information concerning insulin, intermediary metabolism and manifestations, remains obscure. At present, no definite translation of what information is available explains the pathogenesis of the angiopathy associated with its long-term course. The specific problem of retinopathy is further complicated by the intricacies of ocular architecture, the evident variability and dissociation of the pathologic components of the process and the lack of availability of a reliable nonhuman experimental model.

In such a situation, the evaluation of an empirically derived intervention operating by undefined mechanisms is exceedingly difficult. Nevertheless, in over 10 years of experience and observation with pituitary ablation, a picture is emerging which allows certain tentative formulations.

Based on this and other reported experiences, the angiopathic type of retinopathy reaches a sight threatening stage where one eye is already lost after 20 years of diabetes in the population who were recognized as being insulin dependent diabetics at an age close to or just after puberty. It is possible and suggested that the male may be more susceptible than the female. Although intraretinal vascular changes can be demonstrated by the fluorescein retinography technique some years before funduscopic and clinical manifestations appear, once vitreal changes occur and the retinopathy begins to involve neovascular and proliferative growth beyond the retinal surface, an accelerated phase leading to blindness within 2 to 3 years has been initiated.

Hypophyseal stalk section or other methods of pituitary ablation are followed by a series of objectively demonstrable changes in a high proportion of cases. Within days, improvement in vitreous translucency is apparent to both patient, ophthalmologist and interpreter of retinal photographs. After 3 months, disengorgement of dilated retinal veins, resorption of retinal edema, fading of neovascularization and a virtual cessation of vitreal and retinal hemorrhaging can be observed. There is an associated improvement of fluorescein-visualized retinal hemodynamics and a marked reduction in leakage of dye from neovascular formations. At the end of a year, an involutional phase is

achieved, the fibrotic advance has halted, and the proliferative formations have become avascular.

These observations arouse strong suspicions that a humoral factor of either pituitary or hypothalamic origin has been removed or that ablation may have increased the production of a releasing factor. As yet, such hypothetical factor or factors have not been identified. Initially, it appeared that a near totality of endocrine ablation was necessary and, while this consideration appears to be important as a generality, the exceptions are notable and may have important implications. By inference, it appears that none of the replaced target gland hormones are influential. Gonadotropins appear to be exonerated on a circumstantial basis and somatotropin by direct investigation.

The subsidence of leakage from neovascular formations, the resorption of retinal edema and the correlation with the hyaline lesions of the renal glomerulus suggest that the site of action of the hypothetical humoral factor is at the wall of the arterioles and neovessels and that arrest of fibrotic proliferation is a secondary effect. The poorer results in the patients over 40 could be interpreted as the result of a larger component of arteriosclerosis in vessels of patients of this age range.

An uncontrolled experience makes for uncertainty as to the practical usefulness of hypophyseal stalk section, especially in the light of relatively dismal prognosis for activity and life in patients in an advanced stage of a widespread vasculopathy. The disadvantages of compensated hypopituitarism have not been serious or the added requirements for self-care burdensome in our experience and are almost inconsequential in the judgment of patients and physicians if a good ocular result is obtained.

From a comparison of our experience with descriptions of the course of retinopathy of a similar proliferative and neovascular character in patients at an equivalent stage of advancement, we estimate that the prognosis for retention of macular vision has been improved a minimum of twofold at postop intervals beyond 2 years. The major limitations to even more impressive results appears to be the degree and character of already existing proliferation which set the stage for eventual retinal detachment despite induced arrest of hemorrhagic phenomena. Therefore, the implications of this experience in regard to selection of patients beyond those already published are to focus therapeutic attention on those cases where the extraretinal stage of proliferation has just begun and to favor those patients who are under 40 years of age. It is suspected that evidence of arteriosclerosis, advanced beyond that expected for the duration of the diabetes, ought to be considered a negative feature in the evaluation of candidates.

SUMMARY

(1) One hundred and twenty cases of hypophyseal stalk section for angiopathic diabetic retinopathy have been followed from 2 to 9 years. The group was 79 percent male, 21 percent female, and had attained an average age of 34.5 years after an average duration of 19.9 years of diabetes and a 2.3-year duration of retinopathy. Seventy-four percent were already blind in one eye at the time of operation.

(2) The operative mortality was 2.5 percent, and the subsequent death rate, chiefly due to myocardial infarction, averaged 4.5 percent per year through the fifth postop year and then rose to 8 percent per year by the ninth year. Of the 33 deaths, only one appeared to be related to the hypopituitary state.

(3) The visual retention index remained at the 0.9 level through the third postop year and declined to the 0.75 level by the seventh to ninth years. In 32 percent of the sighted eyes, there was improvement in the O'Hare N rating, improvement in the H rating in 15 percent, and improvement in the F rating in 14 percent. A minimum of 16 of the living patients more than 3 years postop were in a stage of total involution of their retinopathy. Patients under 40 years of age at the time of operation had significantly better eye results with an 80.6 percent success rate as contrasted with a 46.9 percent success rate in the older population. The visual prognosis for the group as a whole was estimated to have been doubled.

(4) A significantly positive correlation was found between the degree of hyaline degeneration of the hilar glomerular arterioles on preoperative renal biopsies and the ultimate clinical outcome in regard to retinopathy. No other correlations with 25 other parameters of renal pathology were apparent.

(5) Until a more effective preventive therapy is available, pituitary ablation deserves consideration as a measure of desperation in motivated patients who meet the qualifications for selection.

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CHAPTER 21

Pituitary Ablation for the Treatment of Diabetic Retinopathy[1]

ERNEST J. GREENBERG, M.D.
BRONSON S. RAY, M.D.
A. G. PAZIANOS, M.D.
M. ISAACS, M.D.
B. J. KOVEN, M.D.

Diabetes mellitus has come to be regarded not only as a metabolic defect of carbohydrate metabolism but also as a disease affecting vascular tissue. While the metabolic defect can be controlled by the judicious use of insulin, oral hypoglycemic agents and special diet, the vascular lesions continue to progress, leading frequently to extensive retinal lesions, renal function impairment, coronary heart disease at an early age and peripheral vascular disease.

Following the early encouraging results reported by Luft et al. in 1955 with hypophysectomy for the treatment of diabetic retinopathy, pituitary destruction was used in several medical centers for the relief of this condition. The results have generally been favorable with maintenance or improvement of vision in a major proportion of the groups of patients who underwent such a procedure.

PATIENT SELECTION AND METHODS

Since 1956 pituitary ablation has been carried out at the New York Hospital-Cornell Medical Center on 97 patients with diabetic retinopathy. It was performed surgically in 75 patients including one stalk section, and by means of transsphenoidal Y^{90} inplantation into the pituitary in 22 patients.

After our initial experience with the first 18 patients (*1*, *2*) clinical criteria for operability were established and led to complete elimination of surgical mortality (within 30 days of surgery). These criteria have been published (*2*), but are reproduced here for the sake of completeness of this report.

[1] See appendix D for raw data on individual patients.

Memorial Sloan-Kettering Cancer Center and New York Hospital-Cornell Medical Center, N.Y.

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Age limit

Patients over 40 years of age tolerated the surgery less well, had a high incidence of vascular and renal complication and in general less improvement of their retinopathy following surgery. Very few exceptions were made to this rule and only where the clinical condition was so exceptionally good that such an exception was warranted.

Useful vision in one or both eyes

Hypophysectomy provides no benefit for the patient who is almost sightless as a result of long standing diabetic retinopathy. Recent hemorrhage in an eye which until then had good vision may cause a temporary major visual impairment but is not a contraindication to surgery.

Progression of visual impairment

An effort has been made to select for operation only those patients with progression of retinopathy measured by direct examination over a period of several months by an ophthalmologist or evaluated clinically through a history of repeated hemorrhages and progressive subjective visual impairment.

Absence of retinitis proliferans

While we have observed regression of hemorrhages, exudates and microaneurysms following pituitary ablation, retinitis proliferans has usually not regressed and has frequently led to further visual loss even after surgery in the limited number of patients affected by this type of lesion. Exceptions were made if such lesions were minimal or restricted to one eye.

Adequate renal function

Renal vascular lesions being practically the rule in patients with diabetic retinopathy, great attention was paid to renal function in the selection of patients for pituitary ablation. The following values were considered acceptable for surgery: blood urea nitrogen less than 30 milligrams per 100 cubic centimeters; endogenous creatinine clearance greater than 50 cubic centimeters per minute; urea clearance greater than 50 percent of normal and proteinuria less than 5 grams per 24 hours. There should also be no history of chronic pyelonephritis. A particularly extensive renal function study was carried out before and after surgery in 18 patients (*3*) and is summarized below.

Good cardiovascular function

Patients with severe hypertension, a history of angina pectoris, previous myocardial infraction or cardiac decompensation were considered unacceptable for surgery. Similarly, patients with symptomatic peripheral vascular disease were unacceptable for surgery.

Reasonable intelligence

The ability to understand the hormonal management after pituitary ablation, the management of stressful states and of the change in insulin sensitivity and requirements is an essential criterion in the selection of patients. The need for regular followup and availability of a physician knowledgeable about such a clinical setting is emphasized.

A group of 18 patients, including one who had been treated only by neutron beam irradiation to the pituitary, underwent more extensive investigation of their renal function before and following surgery. They were hospitalized on a metabolic ward. Some, but not always all, of the following parameters were evaluated: urinalysis; quantitative urinary protein; hemoglobin; hematocrit; serum total protein and albumin; serum cholesterol, total and free; total exchangeable potassium (K^{42}); serum electrolytes; blood gases; blood urea nitrogen; serum creatinine; clearances of inulin, PAH, creatinine and urea; percutaneous renal biopsy was also performed by one of us (B.J.K.). The baseline studies were conducted immediately prior to surgery and were repeated 1 to 33 months following pituitary ablation. During the post-operative evaluation all patients were kept on constant full hormonal replacement and on optimal control of the diabetes mellitus with insulin.

Ophthalmological evaluation was obtained prior to surgery and included a measure of visual acuity and a description of the retinal lesions. In addition in most patients it was possible also to obtain retinal photographs as well as composite drawings of the fundus of each eye based on examination through the indirect ophthalmoscope and on the fitting of photographs of multiple adjacent fields of the retina—these served as a basis for comparison with later examinations obtained at intervals of 3 to 12 months following surgery.

SURGICAL PROCEDURE AND MANAGEMENT

Surgical ablation of the pituitary gland was carried out through a transfrontal craniotomy according to a technique previously described (*4*).

Y^{90} implantation into the gland was carried out by the technique described by Forrest et al. (*5*) through a transnasal approach, except in one case in which the technique described by Fraser et al. (*6*), through a paranasal approach was used.

Twenty-four hours prior to surgery the patients were maintained on regular insulin coverage only, without any long-acting insulin.

On the afternoon preceding surgery the patients received 300 milligrams of cortisone acetate intramuscularly in divided doses and following surgery this preparation was given intramuscularly, then orally, in gradually decreasing dosage until a maintenance level of 50 milligrams per day was reached at the end of 10 to 14 days. During the immediate postoperative period regular insulin was given to control the hyperglycemia and glycosuria, and a change to a long acting insulin preparation was effected once the patient was placed on adequate dietary intake and the cortisone dosage approached maintenance level. Anticonvulsants were given in the form of diphenylhydantoin and/or phenobarbital during the postoperative period and were discontinued gradually after discharge from the hospital.

The completeness of the pituitary ablation was based upon the absence of pituitary gonadotrophins in the urine and a fall of the protein-bound iodine level or radioactive iodine uptake to hypothyroid levels.

Replacement dose of a thyroid hormone preparation, estrogens and/or androgens were given to all patients.

Diabetes insipidus was corrected if necessary through the use of nasal insufflation of posterior pituitary powder or, in rare instances, by intramuscular injection of pitressin tannate in oil, 3 to 5 units, at intervals of 1 to 3 days.

RESULTS

An evaluation of the effects of pituitary ablation on the retinal lesion was carried out on the first 78 patients including 56 surgical ablations and 22 Y^{90} implants. Among the first 18 unselected patients there were four postoperative deaths within 30 days of surgery and two additional deaths 4 and 6 months postoperatively from hepatitis and coronary occlusion respectively. Of the remaining 12 patients eight were considered to have shown improvement or arrest of the retinopathy. Thereafter ophthalmological and medical criteria were formulated for the selection of patients for pituitary ablation, and the surgical mortality was completely eliminated. These criteria, however, led us to reject for surgery many patients who could have a chance

to benefit from it were it not for their advanced cardiac or renal function impairment. It was believed that transsphenoidal Y^{90} implantation into the pituitary gland could be more easily tolerated by such patients and this technique was used in 22. Twelve of this group developed complications starting with a CSF fistula in most, with meningitis occurring in eight, five of whom expired as a result of such complications 7 weeks to 11 months after the surgical procedure. This procedure is no longer used.

TABLE I.—*Effect of pituitary ablation on diabetic retinopathy*

Type of pituitary ablation	Number of patients		Results			Uneval-uated	Postopera-tive deaths within 30 days
	Total	Evaluated	Improved	Arrested	Unim-proved		
Surgical	56	47	31	6	10	5	[1] 4
Y^{90}	22	16	5	7	4	6	0
Total	78	63	36	13	14	11	[1] 4

[1] These deaths occured in the early series of 18 unselected patients. In the later series of 38 patients there were no postoperative deaths.

The results are given in appendices C–1 and C–2 and summarized in table I. Sixty-three patients were evaluated out of the 78 reported in the tables. Of the evaluated group 78 percent benefited through regression or arrest of the retinal lesions, and 22 percent were unimproved and suffered progressive deterioration of vision. The last 19 patients were still not evaluated, and there has been no surgical mortality among them.

Several patients underwent photocogulation of retinal lesions months or years after hypophysectomy because of either repeated hemorrhages from one region of the retina or of progression of previously limited retinitis proliferans.

Evaluation of renal function before and after surgery has revealed the following:

BUN: It was normal in 11 patients preoperatively and slightly elevated in seven. It remained normal in nine patients postoperatively.

GFR: The glomerular filtration rate was low in eight of 11 patients preoperatively and decreased in eight out of 10 patients tested postoperatively.

RPF: The renal plasma flow was low in nine of these 11 patients preoperatively and also decreased in eight out of 10 patients tested postoperatively.

ENDOGENOUS CREATININE CLEARANCE was normal in only one of the 11 patients tested preoperatively, and it fell in the majority following surgery.

TEK: The total exchangeable potassium was low in six out of 21 patients tested prior to surgery, and it decreased in 16 patients after surgery.

RENAL BIOPSIES AND AUTOPSIES: Nodular glomerulosclerosis and arteriolar sclerosis were present in all six patients who underwent cutaneous biopsy. There were no significant changes postoperatively.

Of five patients who died and on whom an autopsy was performed, all showed glomerulosclerosis on examination of renal tissue.

DISCUSSION

Vascular disease associated with diabetes mellitus has supplanted the metabolic defect as the major problem in the management of this disease. Untreated diabetic retinopathy carries a high incidence of blindness within a few years of the first development of visual impairment (*7*).

Pituitary ablation has been directed toward the control and relief of this progressive loss of vision resulting from the retinal vascular lesions.

The regression of microaneurysms, exudates, hemorrhages, and sometimes of neovascularization, has been the major improvement noted after this procedure. While we have not randomized our observations between operated and nonoperated patients other observers have carried out such a comparative study and reported the beneficial effects of pituitary abalation (*8*).

Unfortunately a certain amount of irreversible vascular damage is observed in all patients on followup examinations of the retina and this has led in turn to recurrent hemorrhages at various intervals or to progression of retinitis proliferans in a small group of patients. Photocoagulation has been used for the control of these recurrent complications with good results. The generalized regression of the retinal lesions following pituitary abalation appears to be the result of humoral changes following this procedure. The exact nature of the changes and mechanism of action responsible for this improvement is still unclear. Although growth hormone seems to be the most likely agent whose removal results in a decrease in insulin requirement and probably in an improvement of the vascular lesions, this remains to be proved. Furthermore some of the retinal lesions appear to be independent of those humoral changes and have to be treated by other local measures.

The other vascular lesions remain a major cause of morbidity and mortality. Their development and progression does not seem affected

by pituitary ablation. Indeed renal function is usually worse following surgery. This seems to be the result of the endocrine changes in addition to possible progression of the diabetic glomerulosclerosis. The latter, however, is not documented. Coronary occlusion and renal failure have been the major causes of death. Peripheral vascular disease has led to amputation of one limb in two patients and to bilateral amputations in a third one.

Similarly, diabetic neuropathy and associated enteropathy, when present, do not seem to improve following surgery.

The reason of the specific favorable effect of pituitary ablation on the retinal lesions, without any evidence of improvement of other vascular lesions, remains unclear. It is possible that in most of our patients the other vascular lesions have reached an irreversible stage or that our methods of evaluation, still limited in their scope, have not detected fully the visceral and peripheral vascular changes induced by pituitary ablation through the clinical observations and the functional tests which have been carried out.

SUMMARY

The experience with pituitary ablation for the treatment of diabetic retinopathy in 78 patients indicates that a favorable response occurred in more than three quarters of those who were evaluated (63 patients). Y^{90} implantation into the pituitary gland was the method used in 22 of this group of patients but has been abandoned as a technique because of high ensuing morbidity.

Evaluation of renal function in 18 of these patients has been carried out and indicates that a decrease in function follows the surgery. While this does not imply that progressive glomerulosclerosis is the only mechanism of this stage, it emphasizes the need for a good renal function "reserve" before accepting patients for pituitary ablation.

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CHAPTER 22

Transsphenoidol Microsurgical Selective Anterior Pituitary Ablation: A Pathophysiological Investigation of Diabetic Retinopathy [1]

JULES HARDY, F.R.C.S.(c), F.A.C.S.
ALAIN PANISSET, M.D.
ANDRE MARCHILDON, F.R.C.S.(c)
ANDRE LANTHIER, F.R.C.P.(c)

The original observation by Wolter (*1*) of centrifugal fibers in the human optic nerve and retina which originate in the hypothalamus and course through the pituitary stalk could support the hypothesis of a neural mechanism involved in the pathogenesis of diabetic retinopathy and the improvement of this condition following a surgical procedure injuring the pituitary stalk and neurohypophysis.

On the other hand the recent post mortem study by Poulsen (*2*) of his famous patient reported first in 1953 (*3*), has confirmed a close anatomicoclinical correlation between the permanent improvement of her diabetic retinopathy, and the complete and selective necrosis of the anterior lobe of the hypophysis. This would strongly support the hypothesis of a hormonal pituitary mechanism, as already suggested from the classical Houssay's phenomenon. However, the coincidence of these two uncommon clinical conditions has rarely been observed and pathologically verified so that further basic understanding is likely to come from surgically induced similar conditions.

Various methods of hypophysectomy in human beings have been used in the past. Without regard to the various techniques and approaches, they have essentially achieved either a total hypophysectomy or a pituitary stalk section (*4*, *5*, *6*). In the first instance, the problem of neural versus hormonal mechanism is not clarified. Since the pituitary stalk has been sectioned, it is possible that the neural mechanism may have played a major role in the mechanism of improvement of diabetic retinopathy as suggested by Wolter (*1*). But it is well known that an infarction of the anterior pituitary also occurred due to the interruption of the long portal vessels resulting in various degrees of hormonal insufficiency (*7*, *8*, *9*).

[1] See appendix D for raw data on individual patients.

From Notre Dame Hospital and University of Montreal Medical School, Montreal, Canada.

The main purpose of this work was an attempt to reproduce essentially the same anatomopathological condition as in the case of Poulsen. This was possible by refining our routine method of transsphenoidal microsurgical hypophysectomy (most frequently used for advanced metastatic cancer of the breast) to attempt to perform in a series of diabetic patients, when possible, a complete ablation of the anterior lobe of the hypophysis with preservation of the neural lobe and stalk.

SURGICAL TECHNIQUE

The subnasal midline rhino-septal approach to the sella turcica has already been described in detail elsewhere (*10*, *11*, *12*, *13*) and figure 1. It has been used so far in more than 200 cases. The main advantages of this method are a relatively benign trauma, a simple and rapid access to the region and an accurate and magnified visualization of the intrasellar contents using the surgical dissecting microscope. Therefore, surgical treatment can be offered without restriction to relatively aged patients and at a minimal risk to patient with other medical conditions.

Pertinent remarks concerning the possibility of achieving a selective anterior hypophysectomy are based on microscopic anatomical studies of frozen sphenoid blocks from cadavers (*14*) correlated with the anatomical findings during surgery in patients (*15*).

(*a*) The anterior pituitary lobe is surrounded in life by a virtual space which is well identified in the cadaver as a real space filled with venous capillaries between the dural sheath and the hypophyseal capsule. This constant anatomical finding is the basis for the important technical detail of identifying this extracapsular plane of cleavage in order to initiate the dissection of the anterior lobe. The hypophyseal capsule is well recognized under the microscope due to its glistening appearance. Any disruption of this capsule may lead to a false dissection causing hypophyseal fragments to remain in the sella turcica.

(*b*) The posterior lobe, on the contrary, in life and in cadavers, is most of the time firmly adherent to the posterior wall of the sella turcica, being embedded in a shallow depression of the anterior aspect of the dorsum sellae. The line of cleavage between the anterior and the posterior lobe is provided by the intermediate lobe which is a strip of tissue containing many vacuoles filled with colloidlike substance and venous capillaries. Its loose attachment allows the separation between the glandular and the neural lobe.

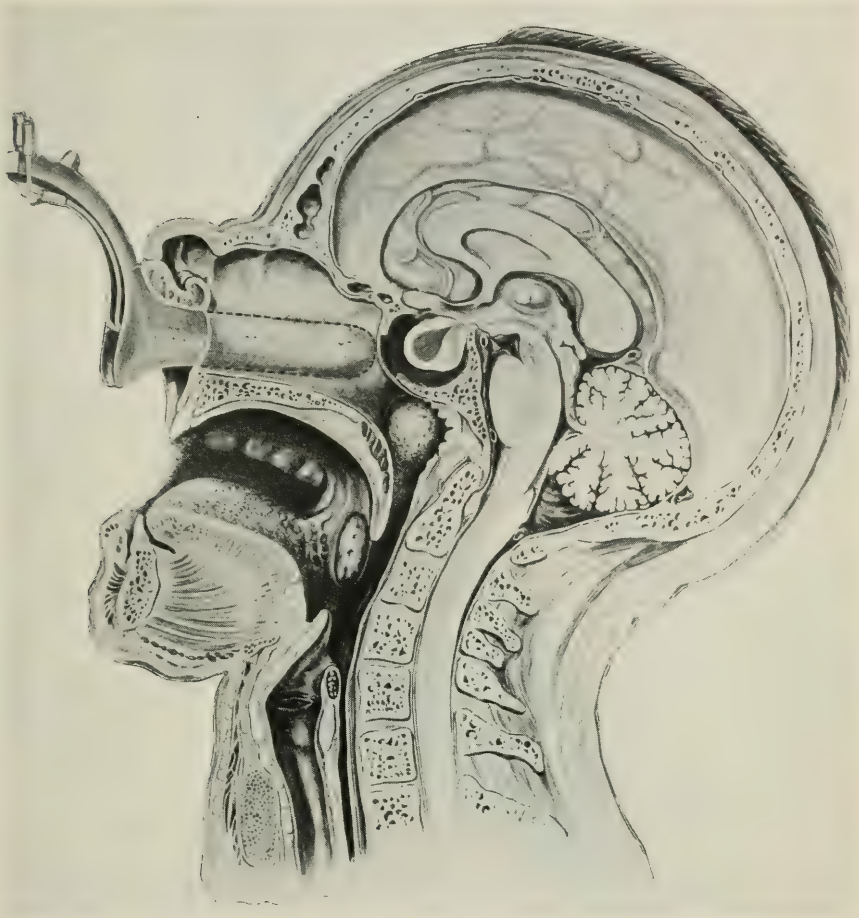

FIGURE 1.—*Schematic illustration of the subnasal, midline, rhinoseptal, transsphenoidal approach to the pituitary.*

Dissection of the anterior pituitary is started along its superior surface and continued until the stalk and the orifice of the diaphragma sellae are encountered. At this moment a small cotton pledget is applied against the stalk which is held backward while the anterior lobe is pressed downward in order to initiate the separation of the two lobes (fig. 2a). The cotton pledget is then further inserted between the two lobes, thus protecting the posterior lobe. The dissection is continued laterally on either side and inferiorly until the whole anterior lobe is completely detached and enucleated (fig. 2b).

When viewed through the operative microscope (x 16) the two lobes of the hypophysis appear quite different in color. Whereas the anterior lobe is yellowish through its glistening capsule and becomes

FIGURES 2 a–c.—*Microsurgical technique of selective anterior hypophysectomy with preservation of posterior lobe and stalk. (Details in text.)*

white under pressure, the more gelatinous appearing neural lobe and stalk are reddish-grey in color due to their rich capillary network. Any incidental remaining fragments are then clearly visible and easily detached. For instance the pars tuberalis sometimes surrounds the pituitary stalk like a collar. It was possible to peel it off easily in some cases. In other cases, when a firm adhesion was present between both hypophyseal lobes it was not possible to perform, as desired, the selective anterior hypophysectomy; then, a low stalk section was carried out with total extracapsular pituitary ablation.

(*c*) Incidental rare anatomical anomalies of the intrasellar contents (low circular sinus, carotid artery, large diaphragmatic orifice) have been observed among the total series of transsphenoidal operations. They have been discussed in another paper along with the technical subtlety of dealing with these anatomical variations (*15*). It must be clearly stated however that under microsurgical exploration these anomalies have been well identified and managed without difficulty or operative complication.

(*d*) An important technical detail has been developed in order to assure an adequate and secure method of sealing the sella turcica following hypophysectomy so as to prevent any possible CSF leak (fig. 2c). The sella cavity is packed with a piece of muscle and the sella window is obliterated with a cartilagenous graft. Careful adherence to technique has overcome this possible complication.

PRE AND POSTOPERATIVE MANAGEMENT

Antibiotic therapy is started the night before the operation: Ampicillin 500 mg. q 6 hours and Coly-Mycin 50 mg. q 12 hours are given intramuscularly during 5 days. The patient is maintained on oral Ampicillin 250 mg. q 6 hours for 10 days. With this protocol we did not have a single instance of infection in this series.

Hormonal substitution therapy is started the night before the operation with cortisone acetate 100 mg. intramuscularly and the morning just before the induction of anaesthesia. Hydrocortisome 100 mg. in physiologic saline solution is given during surgery and repeated twice during the next 24 hours, for a total amount of 300 mg. Then cortisone acetate 50 mg. intramuscularly is given for 5 days and then tapered progressively down to 37.5 mg. orally daily. Insulin is not given the morning of the operation. After recovery from anesthesia, the insulin requirements are determined by frequently repeated urine and blood sugar tests during the first postoperative days. The dramatic reduction in the insulin requirement will be discussed below.

Thyroid replacement therapy is given after thyroid function tests

have been performed around the ninth postoperative day. All patients required l-thyroxin 0.2 to 0.3 milligrams daily.

If the patient presents diabetes insipidus, it is controlled with intramuscular pitressin tannate, five international units in oil solution, repeated as required, usually every 48 hours.

MATERIAL

Thirty patients with progressive diabetic retinopathy have been submitted to transsphenoidal surgical hypophysectomy. There were 17 men and 13 women, all white Caucasians. There were 14 patients below and 16 above the age of 40 (table 1). The mean age of female

TABLE 1.—*Diabetic retinopathy (30 cases)*

Age: 22 to 61.
Sex: 17 men, 13 women.
Age groups:
- Below 40:
  - 20 to 29: six.
  - 30 to 39: eight.
- Above 40:
  - 40 to 49: six.
  - 50 to 59: nine.
  - 60 to 69: one.

patients was 46.1 years (from 24 to 61), and of males 39 years (25 to 56). Fifteen patients had a juvenile type of diabetes with a mean age of 31.5 years for female and 31.7 years for male patients. Fifteen patients were suffering from an adult-type diabetes with a mean age of 54.8 years for females and 50.8 years for male patients. Among the 15 juvenile diabetics, the insulin requirements were unstable in 13 cases; whereas among the 15 adult diabetics only two were unstable, and eight patients received no insulin. In most of the patients the diabetes was of more than 10 years duration (table 2).

TABLE 2.—*Diabetic conditions*

	Cases
Type:	
Juvenile (onset <30 years)	15
Adult (onset >30 years)	15
Duration:	
<1 year	3
1 to 10 years	6
10 to 20 years	13
>20 years	8
Insulin requirements:	
15 juveniles:	
Unstable	13
Stable	2
15 adults:	
Unstable	2
Stable	5
Nil	8

In relation to the severity of the retinopathy, the patients were graded according to the standard classification also coded on IBM cards according to the classification suggested by Lee et al. (*16*). The conversion into the O'Hare classification [1] is shown in appendix D. Also, four patients had a cataract in one eye, and six, in both eyes. No patients had ever suffered from glaucoma. Other medical conditions found in some patients are mentioned in table 3. One had uveitis in one eye (rubeosis iridis).

TABLE 3.—*Other conditions*

Cataract in 1 or both eyes	10
Nephropathy	8
Juvenile (3 renal insuff., K.W.)	5
Adult	3
Neuropathy	10
H.T. and cardiovasculopathy	6

RESULTS

From the surgical point of view, there was no operative mortality and not a single instance of postoperative infection. Only one case had a rhinorrhea which was easily corrected. This was one of the earlier cases before we began using the present technique of sealing the sella floor with cartilagenous graft.

All the 22 patients who required insulin before hypophysectomy showed a marked reduction to less than half of their preoperative dosage. Six required no more insulin at all. Among the 15 patients who had unstable requirements prior to hypophysectomy, two have completely suppressed their insulin need, whereas 12 others have stabilized their requirement. One remained unstable (table 4).

TABLE 4.—*Insulin requirements (22 cases)*

Unstable (13 juvenile)	15
Stable	7
All reduced (last F.–UP):	
Complete suppression	6
To <50 percent of preop dosage	16

NOTE.—All but 1 stable.

From the subjective visual point of view, 18 patients reported visual improvement quite soon after hypophysectomy: 10 within 5 days, five within 10 days, three within 15 days. Seven others noticed some improvement in their vision soon after discharge and reported this to the ophthalmologist at their first postoperative visit after 3 months (table 5). In the remaining five cases, one patient had no visual trouble

[1] O'Hare Classification, p. XXI.

TABLE 5.—*Onset of visual improvement (25 cases)*

Before discharge	18
Within 5 days	10
Within 10 days	5
Within 15 days	3
At 1st visit (3 months)	7

before hypophysectomy (case 14). A competent ophthalmogist had observed diabetic retinopathy which progressed rapidly to grade $BH_0N_1F_0$, O.U.[1] At the last examination 10 months after hypophysectomy the retinopathy improved to $BH_0N_0F_0$ for O.D. and to completely normal for O.S. with a visual retention index of 1.[2] The four other patients were neither improved nor worsened from the visual point of view. Therefore 25 cases were favorably influenced by hypophysectomy in the early postoperative period, four were uninfluenced, none were worsened.

After a longer followup period, the average visual retention index for adult type diabetic patients was 0.78 (23 eyes), and 0.82 for juvenile type patients (30 eyes).

The same index calculated on eyes showing no neovascularization was 0.76 (five eyes) for juvenile patients and 0.82 (12 eyes) for adult-type patients. Calculated again on the eyes showing some degree of neovascularization, the mean visual retention index was 0.73 (22 eyes) for juvenile and 0.69 (11 eyes) for adult-type diabetic patients.

These results point toward the best prognosis on eyes without new vessels in adult type patients. We have excluded from this correlation study the eyes which did not have sufficient acuity to read at least the biggest letters on the visual charts.

METHODS OF ASSESSMENTS OF PITUITARY ABLATION

With the exception of growth hormone levels which were carried out only in a few patients and of urinary gonadotrophin determinations, direct assay of pituitary hormones are still unavailable for routine clinical work. Instead the routine clinical investigation were devoted to the function of the target organs: gonads, thyroid gland, and adrenal cortex. The laboratory studies are summarized in the legend of the tabular summary (appendix D).

From the practical point of view, the plasma and urinary corticoids could not be assessed postoperatively since replacement corticoid therapy was provided during the surgical ablation of the hypophysis

[1] O'Hare Classification, p. XXI.

[2] See p. 256–7 or discussion of visual retention index.

and was maintained afterwards. Therefore the only valuable methods were the thyroid and gonadal functions which could be studied without threatening the patient's condition. In the present series, low or undetectable gonadotrophins (less than 10 MU) were found before hypophysectomy in 11 patients. This determination was then of no value postoperatively. In five cases, the gonadotrophins were significantly detectable preoperatively (+40 MU), and they were negative after hypophysectomy. The others were not assessed.

The thyroid function studies were available and significantly reduced in 22 cases. As mentioned above, all the patients who required insulin prior to surgery had a significant reduction in their requirements postoperatively which was interpreted as a valuable criterion of pituitary insufficiency.

It must be stated that the target organ assays must be judged with caution because of the wide individual variations that can occur in diabetic patients. On the other hand, if endocrine studies are reliable in confirming the degree of pituitary insufficiency, we cannot deny the significant value of other methods available because of the surgical technique described above. Two other criteria are obviously valuable prior to the endocrine assays in the postoperative period. First the open surgical procedure allows the surgeon to verify directly during the operation if the sella turcica is completely empty. Moreover the use of the surgical microscope allows clear visualization of the intrasellar contents so that any remaining microscopic fragment of pituitary tissue can be removed. In those circumstances, when there has been no difficulty in achieving a complete extracapsular enucleation of the pituitary, this is in our opinion the most valuable criterion. Secondly, the histological examination of the removed gland confirms the completeness of pituitary ablation. In this series of diabetic patients we found occasionally a very soft gland which could not be completely excised *en bloc*. Such a gland has been removed by fragments or sucked out. Since most of the tissue was lost in the sucker, we paid much attention to revise the sella under high power magnification and peel off the remaining thin capsule of the pituitary, therefore assuring a complete removal of the capsule in which may remain some pituitary tissue.

From the histological point of view, the pathological verification of the material from those 30 cases has shown that, in 11 cases, a total surgical extracapsular complete enucleation of the pituitary was accomplished after stalk section. In those cases the plane of cleavage between the anterior and posterior lobes was not easily identified and the posterior lobe was not firmly attached to the sella turcica. In the 19 other cases, the anatomical configuration of the sella turcica, the shape of the gland, its firmness and loose attachment have made possible a

complete selective ablation of the anterior lobe only. The posterior lobe and stalk were clearly visualized and left in place. In seven of these, the histological study has revealed the presence of a few bundles of neural tissue attached to the anterior pituitary. In the other 12 the anterior pituitary was complete and there were no fragments of posterior lobe. Nonetheless it is relevant to notice that amongst the attempts to perform a selective anterior pituitary ablation, seven out of the 19 patients presented diabetes insipidus requiring Pitressin. In the series of total hypophysectomy after low pituitary stalk section, only one case presented diabetes insipidus (table 6). We now have the answer to this

TABLE 6

HX	Histology	D. I.
Subtotal (19 cases)	Anterior lobe only (12)	4
	A.L. + few P.L. fibers (7)	3
Total (11 cases)	A.L. + P.L. + stalk section (11)	1

paradoxical phenomenon. Since the selective ablation of the anterior lobe required manipulation of the stalk in order to initiate the separation of the anterior lobe from the posterior, it is felt that the cotton pledget accomplished ischemic pressure to the stalk and probably some degree of traction due to posterior displacement and that this was responsible for the suppression of hypothalamic-hypophyseal function of ADH secretion. On the other hand, when the pituitary stalk was sectioned low near the surface of the gland before the initiation of its detachment, ischemic disturbance in the neurohypophyseal track was less likely to occur. From the practical point of view, it is now felt that minimal manipulation of the stalk will avoid the production of diabetes insipidus. Therefore we would recommend gaining access to the stalk at the initiation of the dissection, performing a low stalk section and then pursuing the enucleation of the gland or of the anterior lobe as is often possible. Obviously if the posterior lobe remains firmly attached to the anterior aspect of the dorsum sellae, it is not necessary to remove it since it will require a delicate maneuver with small curettes that might produce unnecessary bleeding.

In two cases a continuous oozing during surgical ablation of the hypophysis did not permit an accurate revision of the empty sella; although the gland was removed piecemeal (anterior lobe), both cases presented complete endocrinological hypopituitarism. In three other cases in whom the pituitary was histologically incomplete due to the soft consistency of the tissue that was partly suctioned out, both anatomical revision of the sella and the endocrinological studies confirmed the completeness of pituitary ablation. In the remaining 25 patients in whom both anatomical and histological verification

were completed, the postoperative endocrinological assays confirmed a thyroid function reduction in 22, whereas in three the thyroid determinations were not lowered enough to assure a complete pituitary ablation by endocrinological criteria at the time that they were performed, although it was on the anatomical basis.

The relationship of clinical results to degree of pituitary ablation can only be evaluated in this group of patients on the basis that they all had a complete anterior pituitary insufficiency requiring hormonal replacement. It would seem however that the abruptness of the surgically induced hypopituitarism is also an important factor in the mechanism of improvement of the subjective vision together with the rapid disappearance of retinal and vitreous edema, the recent exudates and hemorrhages and even the new vessel formation. On the other hand, the "waxy" exudates and the fibrotic lesions in the retina and vitreous are not significantly modified after hypophysectomy. One patient also had rubeosis iridis which did not change.

As to the comparison between the groups of total versus selective anterior pituitary ablation, the results were equal. In the 11 cases with total hypophysectomy, the visual retention index was 1 in 12 of the 22 eyes (54.5 percent). In the 19 cases with selective anterior hypophysectomy, the visual retention index was 1 in 19 eyes (53 percent). On the total of 58 eyes, the visual retention index was 1 in 31 eyes with an average result of 53.5 percent.

In discussing the fundamental pathogenetic mechanism of improvement of diabetic retinopathy, the neural hypophysis cannot be excluded from the group of cases who had a total hypophysectomy. Even in the group of selective anterior hypophysectomy, those who presented diabetes insipidus have had some degree of ischemic disturbance in the hypothalamo-neurohyphyseal tract due to manipulation of the stalk during dissection.

The remaining 12 cases who had no diabetes insipidus can be considered an anatomicoclinical reproduction of the case of Poulsen, and therefore would provide further evidence to support the hypothesis of a selective hormonal mechanism in the pathogenesis of diabetic retinopathy and the improvement of this condition following complete and abrupt suppression of anterior pituitary function.

Because of the dramatic reduction of the insulin requirement immediately following surgery, it would seem that a fast acting diabetogenic factor has been removed. Whether this is growth hormone or a closely related biochemical compound remains to be shown. At least, we know that the growth hormone levels are abruptly reduced in the minutes following pituitary ablation. Much attention has been paid to the recently discovered and synthesized lipotrophic hormones; these latter

substances could also be responsible since six cases who had an elevation of triglycerides showed a reduction to normal levels following hypophysectomy.

Among the other manifestations of diabetes mellitus, definite improvement of peripheral neuropathies has been observed in some patients.

At any rate, this clinical experimental study which was carried out in an attempt to clarify some aspects of the pathophysiological mechanism of diabetic retinopathy supports the hypothesis of a purely hormonal anterior pituitary mechanism rather than a neural mechanism.

SUMMARY

The pathophysiological basis of diabetic retinopathy was investigated in an experimental clinical series of 30 patients, including 15 juvenile and 15 adult-type diabetics.

Refinement in the microsurgical dissection of the pituitary through an open transsphenoidal midline approach permitted a selective and complete ablation of the anterior pituitary in 19 cases. The other 11 cases had a total hypophysectomy after low stalk section.

The hypothesis of a neural mechanism suggested by Wolter could have been supported in those cases who had an anatomical or functional involvement of the neurohypophyseal tract. The 12 other cases with complete anterior pituitary insufficiency served as an experimental model which reproduced essentially the same anatomicoclinical condition as in the case of Poulsen, and support the hypothesis of a pure hormonal anterior pituitary mechanism responsible for the improvement of the diabetic retinopathy.

The transsphenoidal anterior midline approach to the sella turcica which has proven to be a benign nontraumatic procedure, can be offered not only to relatively aged patients but also with less restriction to patients suffering from other pathological conditions. This is most important, since in our series several of those patients were improved.

The microsurgical exploration of the sella turcica provides an adequate exposure through which it is possible to recognize the rare instances of anatomical variations. It also assures immediately the surgeon of the completeness of the extracapsular pituitary removal which is essential in order to obtain the maximal beneficial clinical result. Abruptness and completeness of anterior pituitary suppression seem to be the most important factor responsible for rapid improvement of the vision and of the pathological fundus of diabetic retinopathy.

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CHAPTER 23

Pituitary Suppression in Diabetic Retinopathy by Proton Beam in Surgically "Unfit" Patients [1]

RAYMOND N. KJELLBERG, M.D.
J. WALLACE McMEEL, M.D.
NANCY McMANUS, R.N.
ANDREAS M. KOEHLER

INTRODUCTION

The Bragg peak of the proton beam has been used to induce pituitary suppression in 171 procedures in diabetics with progressive retinopathy threatening blindness. Because the procedure has been associated with no mortality and modest morbidity, it has been feasible to apply it to such an appreciable number of patients, nearly all of whom would not have been candidates for the surgical stress of conventional procedures such as craniotomy. Because craniotomy-stalk section or hypophysectomy tends to be limited to roughly 20 to 30 percent of diabetics with active deteriorating retinopathy, the group reported herein tends to represent a wider spectrum of patients with retinopathy, although they are not normally distributed since favorable, "surgically fit" cases had usually been removed for craniotomy-stalk section or subtotal hypophysectomy. Because the outlook of this group has been considered compromised by the prospect of disability and death in a few years, it has seemed advantageous for humanitarian and economic reasons to avoid prolonged hospitalization and convalescence. Proton-treated cases, after evaluation, are hospitalized 2 or 3 days for the stereotaxic procedure and convalescence and return to their occupations ordinarily the following week.

It is ordinarily considered that some hormonal pituitary factor when terminated induces clearing of the vitreous, regression of neovascularity, and arrest of new hemorrhages. However, the retinopathic process is complicated, exhibiting in many combinations of various features and progressing apoplectically or inexorably. The pituitary factor is not yet identified with the clarity which seems to be critical,

[1] See appendix E for raw data on individual patients.

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and the known ones are less than constant when correlated with a specific retinal effect. Considering the number of cases available for study and the wide spectrum of pathology they represent, we have studied our material with these objectives in mind:

(1) To learn the relation of ophthalmologic and endocrine factors influencing ophthalmologic results.

(2) To establish preoperative criteria that would aid in patient selection for a given operative technique.

METHOD

Patients, Material

The patients in the present study were treated with the 160-million-electron volt (Mev) Harvard Cyclotron. Before cyclotron treatment, patients are admitted to a hospital for thorough preoperative evaluation.

The premedicated patients are taken to the cyclotron, and a stereotaxic head frame is affixed to the skull under local anesthesia (fig. 1). The alignment of the proton beam within the pituitary fossa is con-

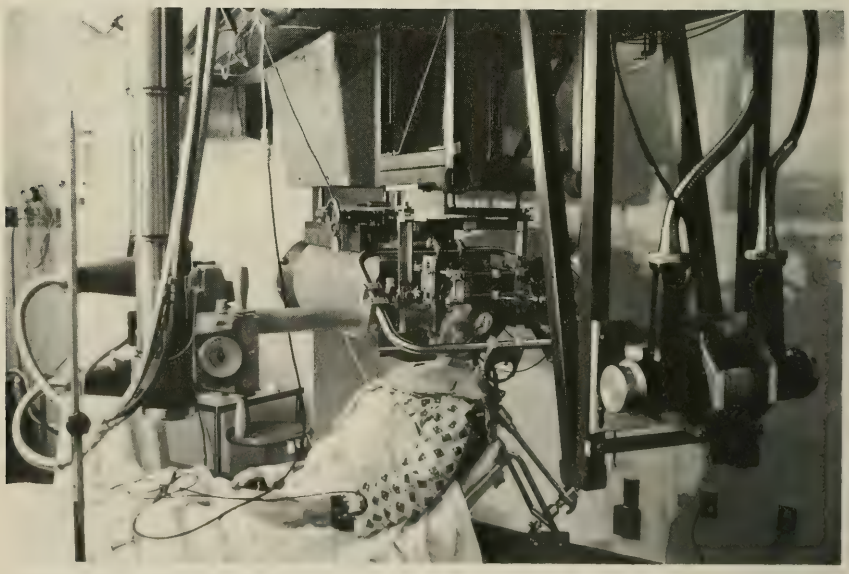


FIGURE 1.—*A patient under local anesthesia is being treated by the proton beam entering from the background. X-rays are used for alignment of the pituitary target, and an exposure of the proton beam on the X-ray film confirms the relation of the beam to the intrasellar contents.*

firmed by exposure of a Polaroid film to an X-ray source and to the proton beam. The radiation dose is administered so that there is less than 1 percent chance that the visual pathways will receive 2,000 rads. We align the beam with the Bragg peak centered in the anterior portion of the sella turcica, so that the anterior two-thirds of the sellar contents get a point dose of 10,000 rads or more to the anterior, inferior, posterior, and lateral margins to be destroyed by radionecrosis, sparing the posterior lobe. Small corrections are introduced in the measurements to account for the passage of the beam through brain, other soft tissue and bone at the side of the head.

In treating diabetic patients, we normally now use 12 portals of entry, six on each side of the head. The design of the stereotaxic apparatus allows the head to rotate about the target point in the sella turcica. A water-filled adjustable absorber is used to control the depth of penetration of each beam. At present a nominal dose, usually of 12,000 rads, is chosen although this dose has previously varied between 8,000 and 15,000 rads. The computer determined point dose distribution to the pituitary gland and surrounding structures, derived from measurements with a silicon diode detector, is shown in figure 2. A portal diameter of 7.0 millimeters can be manipulated to fit most normal pituitary fossae, adjusting the nominal dose if need be. Scalp doses range between 400 and 1,300 rads.

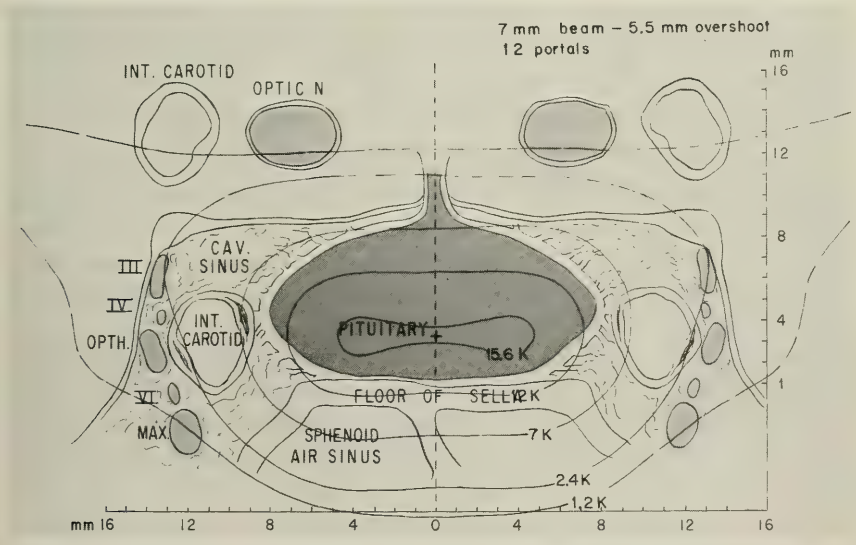


FIGURE 2.—*The isodose curve measured by a silicon diode detector (¼mm² cross section) is computer-determined to a treatment plan to keep the radiation dose to the optic nerves below 2,000 rads. The oculomotor nerves may be as close as 2mm lateral to the pituitary gland and in those instances received a higher dose than shown in the diagram. (K in the figure=Kilorads.) The major bulk of the anterior two-thirds of the gland itself receives over 10,000 rads.*

The entire proton beam treatment is completed in approximately one and a half hours, during which the patient is awake and responsive. After operation, patients usually remain in the hospital for 2 or 3 days. With the exception of trivial tenderness at the sites of the drill rod applications, the observation period is uneventful. Instructions for care and followup are given.

To date we have done 171 stereotaxic Bragg peak proton hypophysectomies on 166 patients. This report covers 157 procedures on 152 patients treated between May 1962, and September 1967. The followup was variable in these patients. Because of the irregular latency in onset of hypopituitarism varying from weeks to many months, no postoperative data are obtained during the primary hospitalization. Nearly all come from outpatient visits, a large number of which were done by physicians other than our group. Ophthalmologic grading and metabolic followup are thereby heavily compromised. In assembling this material we have included all the data documented by a qualified physician. Inevitably such gaps in data produce a bias, but we cannot correct or define it. We have not considered patients' subjective replies suitable as critical quantitative data.

The data were placed on punch cards and sorted according to digitized terms. Of these 152 patients, 84 were men and 68 were women. Their ages at onset of diabetes and treatment were as follows:

	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79
Onset of diabetes	23	66	25	18	13	9	3	0
Treatment	0	0	22	42	47	32	12	2

Nine patients had previously been operated with the intention of inducing pituitary suppression. Seven of these had craniotomy and subtotal hypophysectomy without implantation of a mechanical barrier below the hypophyseal stalk. One patient had craniotomy-stalk section with implantation of a mechanical barrier, and one patient had open transsphenoidal hypophysectomy.

These patients were largely unfit for conventional surgical procedures. The study was instigated largely through the motivation and with the collaboration of Dr. Richard A. Field as an alternative to craniotomy-stalk section, because at that time about three-fourths of patients seen with the ophthalmic indications for pituitary suppression were physiologically or psychologically unfit for the stress of a major surgical procedure (*1*). All of the original patients and most of the later ones were therefore rejects from a group evaluated for the more stressful procedure (*2*). The policy at our unit continues to favor stalk section in appropriate cases, which is performed by Dr. William H. Sweet, Chief of the Neurosurgical Service. A small num-

ber of the patients, 10 in all, would have been suitable for craniotomy but specific request for stereotaxic proton hypophysectomy had been made by the referring physician. The distribution of complicating factors is as follows:

	Number of cases	Percent
Nephropathy	99	63
Cardiac disease	93	61
Hypertension:		
>160/100	71	48
>140/90, <160/100	31	21
Normal	46	31
Neuropathy	119	76
Refused craniotomy	6	4
Failure of previous surgical attempt at pituitary suppression	9	6
Surgically "fit"	10	7

The percentages add up to over 100 percent because the categories overlap, and the processes frequently coexist.

Ophthalmologic evaluation and followup has been done by one of us (J. W. McM.) and/or his associate, Dr. Pei Fei Lee, in the majority of cases using the classification of the latter (*3*). In general, similar ophthalmic criteria are used for proton treated patients for craniotomy stalk section patients, namely, unequivocal demonstration of progressive retinopathy of disease and visual loss. Examination of both eyes is done, grading visual acuity, ocular tension, angiopathy (particularly neovascularization), exudates, fibrous proliferation, hemorrhages, extraocular motility, optic nerve, retinal detachment, cataracts, and rubeosis. Photographs and hand drawn retinal maps are usually made, the Schepens binocular indirect ophthalmoscope being used for

CHART I—*Definitions*

Totally blind: No light perception (NLP). Scored by method described below as 0.00.

Legally blind: Visual acuity 20/200 or less.

Scored as follows:

20/200	0.10
20/400	.05
Count fingers (CF)	.03
Hand movements (HM)	.02
Light perception (LP)	.01

Useful Vision: Better than 20/200. Scored as a decimal; e.g., 20/40=0.50.

Visual Acuity (VA) Ratio: $\frac{\text{postoperative VA}}{\text{preoperative VA}}$

Therefore—

VA Ratio greater than 1.0: improved.

VA Ratio equal to 1.0: unchanged.

VA Ratio less than 1.0: worse.

Visual Retention Index: Number of months vision retained following therapy divided by the number of months following therapy.

CLASSIFICATION OF DIABETIC RETINOPATHY MODIFIED FROM LEE, McMEEL ET AL. (*3*)

ANGIOPATHY

		O'Hare classification [1]
A_1	Not present	
A_2	Mild	N_1
A_3	Moderate	N_1
A_4	Advanced	N_2
A_5	Far advanced	N_2

PROLIFERATIVE RETINOPATHY

P_1	Not present	F_0
P_2	Mild	F_1
P_3	Moderate	F_2
P_4	Advanced	F_2
P_5	Far advanced	F_2

VITREOUS HEMORRHAGE

V_1	Not present	H_0
V_2	Mild	H_1
V_3	Moderate	H_1
V_4	Advanced	H_1
V_5	Far advanced	H_2

Angiopathy Ratio (A Ratio): $\frac{\text{preoperative angiopathy grade}}{\text{postoperative angiopathy grade}}$

Therefore—

A ratio greater than 1.0: improved.
A ratio equal to 1.0: unchanged.
A ratio less than 1.0: worse.

Proliferation ratio (P ratio): $\frac{\text{preoperative proliferation grade}}{\text{postoperative proliferation grade}}$

Therefore—

P ratio greater than 1.0: improved:
P ratio equal to 1.0: unchanged.
P ratio less than 1.0: worse.

Percent of preop insulin: $\frac{\text{postoperative value-units}}{\text{preoperative value-units}}$

Less than 100 percent represents a fall in insulin requirement.

Percent of preop PBI: $\frac{\text{postoperative value-}\mu g\%}{\text{preoperative value-}\mu g\%}$

[1] O'Hare Classification, p. XXI.

the latter. We have treated no patient without visual loss preoperatively. The progress of the disease is confirmed by serial examination and must show deterioration of vision, worsening of angiopathy, or new hemorrhages.

If the retinopathy is primarily exudative or fibrotic with a minimum of new vessel formation, proton hypophysectomy is contraindicated, as pituitary ablation is not considered to have effect on the progression of these features. If there is sufficient traction on the retina to produce a secondary retinal detachment, the chances that proton hypophysectomy will successfully maintain vision are reduced. This is particularly so if the detached area is adjacent to the macula.

Other signs of vitreous shrinkage with vitreo-retinal adhesion also lessen the prognosis for success. These include preretinal or vitreous hemorrhage, elevated tufts of neovascular tissue, and visible membranes in the vitreous extending to areas of neovascularization. The distribution of degree of angiopathic and proliferative change is shown in chart II where the large majority are grades A3, A4 (O'Hare N_1, N_2) and P2–P4 (O'Hare F_1, F_2).

The determination whether a patient is to be proton treated rather than stalk section treated is largely on the basis of nonophthalmic criteria; namely, the patient's general condition. Advanced age, heart disease, renal disease, and other conditions are treated more extensively elsewhere in this text. Occasionally, in a borderline case with rapidly progressive ocular disease, stalk section is favored because of the immediate induction om hypopituitarism. At the time in our hospital

CHART II—*Preoperative grades of angiopathy and proliferation—Number of eyes in each*

O'Hare grade			N_1		N_2		
	Our grade	A_1	A_2	A_3	A_4	A_5	Total
F_0	P_1	2	4	20	6	2	34
F_1	P_2		4	41	21	4	70
F_2	P_3			19	29		48
	P_4	1	1	15	28	5	50
	P_5			3	4	2	9
	Total	3	9	98	88	13	211

when a ratio of cases unfit for craniotomy-stalk section was three out of four, these were immediate candidates for proton hypophysectomy.

The historical, clinical, ophthalmologic, and endocrinologic data were put on punch cards and sorted by an IBM sorter. For the sake of such entry, whenver possible the data were coded in a digital system. A description of terms and the digital equivalent is included in "Chart I—Definitions." We have, however, made a vigorous effort to avoid creating arbitrary categories prior to the analysis to avoid the inevitable bias so created. Visual acuity, for example 20/30, would be recorded as 0.67. Classification of retinopathic findings is digitized with the digit 0 avoided so that ratios between, for example, degree of angiopathy before and after therapy could be computed. We have computed such ratios so that values greater than 1.0 represent improvement, equal to 1.0 represent no change, and less than 1.0 represent worsening, and the degree of change is shown by the magnitude of the ratio.

The central objective of the study is vision, and, in the assessment which follows, we seek to relate factors which may be relevant.

Ophthalmology

It is considered that the process in diabetic retinopathy includes the development of new vessels often extending out into the vitreous which may bleed. Hemorrhages of varying degrees may reabsorb or recur. Parallel to the neovascularization, fibrous proliferation proceeds with various relations to the vitreous and retina and may obscure or detach the retina. We have analyzed our eyes according to degrees of angiopathy and proliferation in chart II prior to proton hypophysectomy. It is seen that only two eyes (A1, P1) were free of both angiopathy and proliferation, 34 eyes had no proliferation (P1) but only 3 had no angiopathy (A1). Most of the eyes had advanced disease (N_2 F_2–O'Hare, 140/211 = 86 percent.)

Effect of Treatment on Angiopathy

In chart III angiopathy ratios (preop grade/postop grade) are plotted against the preoperative grades of both angiopathy and proliferation. In these eyes the great majority show arrest (ratio $=1.0$) or improvement (ratio >1.0). It must be noted, however, that instances in which obscuring hemorrhages occurred, no grading of the postoperative eyes would be available. Further, hemorrhage presum-

CHART III.—*Average angiopathy ratios—Relation of preoperative angiopathy and proliferation grades in 87 eyes*

O'Hare grade			N_1		N_2			Numbers of eyes		
	Our grade	A_1	A_2	A_3	A_4	A_5	Average	>1.0	=1.0	<1.0
F_0	P_1	0.75 (0.5–1.0)	1.00 (1.00)	1.09 (0.8–1.5)	1.00 (1.00)	1.2 (1.2)	1.05	4	14	2
F_1	P_2		1.00 (1.0)	1.21 (1.0–1.5)	1.31 (1.0–2.0)	1.0 (1.0)	1.20	10	15	—
F_2	P_3		1.12 (1.0–1.5)	1.19 (1.0–1.3)			1.16	7	9	—
	P_4		1.00 (1.0)	1.07 (1.0–1.5)	1.22 (0.5–2.0)	1.62 (1.0–2.5)	1.24	10	11	1
	P_5		0.75 (0.7–0.8)	1.30 (1.3)	1.2 (1.2)		1.00	2	—	2
	Average	0.75	1.00	1.12	1.23	1.32	1.156			
Numbers of eyes	>1.0	—	—	12	16	5		33	—	—
	=1.0	1	4	31	9	4		—	49	—
	<1.0	1	—	3	1	—		—	—	5

NOTE.—Figures in parentheses represent range.

333-611 O—69——19

ably can occur in eyes in which the angiopathy is improving. Only five eyes showed worsening of angiopathy. In general the more severe the angiopathy, the greater the improvement. Grade A1 (none) angiopathy can only get worse, accounting for the ratio of less than 1.0. A pattern is less clear with respect to the influence of increasing severity of proliferation. In P5, worst grade, only four eyes limit the significance of the average angiopathy ratio of 1.0. In general it seems the angiopathy arrests or improves fairly independently of the preoperative grade of proliferations.

Effect of Treatment on Proliferation

In chart IV proliferation appears to be nearly never improved. The two instances in which improvement in proliferation were noted could have been irregularities in the estimate of the observer. The proliferation remains unchanged (ratio $=1.0$) twice as frequently as it gets worse. High-grade proliferation (P4) infrequently worsens because it is nearly end stage (P5). The degree of angiopathy has an indifferent relation to the outcome of the proliferation. The frequency of arrest of proliferation (66 percent) may provoke the question whether it is related to treatment or independent of it.

Relation of Preoperative Angiopathy and Proliferation to Outcome of Vision

To aid in selection of potentially favorable candidates for therapy, we studied the visual acuity ratio (VA ratio is postop visual acuity/preop visual acuity). We chose use of division to produce a ratio rather than addition-subtraction of grades, to amplify the degree in those instances in which the change was greater than a single grade. Chart V shows no consistent pattern of response of visual acuity with increasing severity of either angiopathy or proliferation.

Chart VI shows the degree of correlation between the angiopathy ratio and visual acuity ratio. In general many cases show the expected correlation; namely, that improved angiopathy is associated with improved vision. Of great interest are those which do not show the expected correlations. In only one instance did vision improve as angiopathy worsened, but there are few instances of angiopathy worsening after treatment (chart III) from which to judge. More to the point are those large number of cases in which angiopathy improved (angiopathy ratio >1.0) but vision worsened (VA ratio <1.0); namely

CHART IV.—*Average proliferation ratios—Relation of preoperative angiopathy and proliferation grades in 96 eyes*

O'Hare grade			N_1		N_2			Number of eyes		
	Our grade	A_1	A_2	A_3	A_4	A_5	Average	>1. 0	=1. 0	<1. 0
F_0	P_1	0. 65 (0. 65)	1. 0 (1. 0)	0. 71 (0. 3–1. 0)	0. 30 (0. 3)	0. 30 (0. 3)	0. 65	—	8	11
F_1	P_2			0. 85 (0. 4–1. 0)	0. 90 (0. 6–1. 0)	1. 00 (1. 0)	0. 89	—	22	11
	P_3			0. 97 (0. 8–1. 0)	0. 89 (0. 7–1. 0)		0. 92	—	10	6
F^2	P_4		1. 0 (1.0)	0. 96 (0. 8–1. 0)	0. 97 (0. 7–1. 0)	1. 15 (1. 0–1. 3)	1. 00	2	19	3
	P_5			1. 0 (1. 0)	1. 0 (1. 0)	1. 0 (1. 0)	1. 00	—	4	—
	Average	0. 65	1. 00	0. 86	0. 89	0. 99	0. 90			
Numbers of eyes	>1. 0	—	—	—	—	2		2	—	—
	=1. 0	1	2	30	24	6		—	63	—
	<1. 0	1	—	17	12	1		—	—	31

NOTE.—Figures in parentheses represent range.

19 cases or 21 percent. We considered that although hemorrhages may recur in spite of improving angiopathy, there are several causes of visual worsening in these cases.

Relation of Preoperative Visual Acuity to Outcome of Vision (Visual Acuity Ratio)

Chart VII (upper figure) shows the visual acuity ratios for each grade of preoperative visual acuity and the numbers of eyes in each. The lower figure in percent of eyes for each preoperative VA grade is more readable. In general, although the variations between individual VA grades is high, over one-third are in the range $\geqq 1.0$ and another one-third holding at the >0.5 to <1.0 level. The data indicate that eyes with severe impairment of vision preoperatively have a good prospect of holding or improving vision.

Visual Acuity Ratio in Relation to Other Ocular Findings

Initially we sought to identify those factors evident at the time of the preoperative examination which could aid in favoring a satisfactory outcome. Although we have treated a number of "unfit" patients in whom we felt the outlook was rather dismal both from an ophthalmologic and life expectancy aspect, we have performed the procedure, recognizing uncertainty of outcome and the patient's wish for some therapy.

Neverthless, we try to appraise patients of their reasonable expectations as well as we can. We are eager to exclude clearly hopeless patients from an unnecessary procedure in spite of the low stress.

Chart VIII shows the visual acuity ratio in groups of eyes with various other ophthalmologic findings. The groups are improved, arrested, reduced and blind, according to the VA ratios as shown.

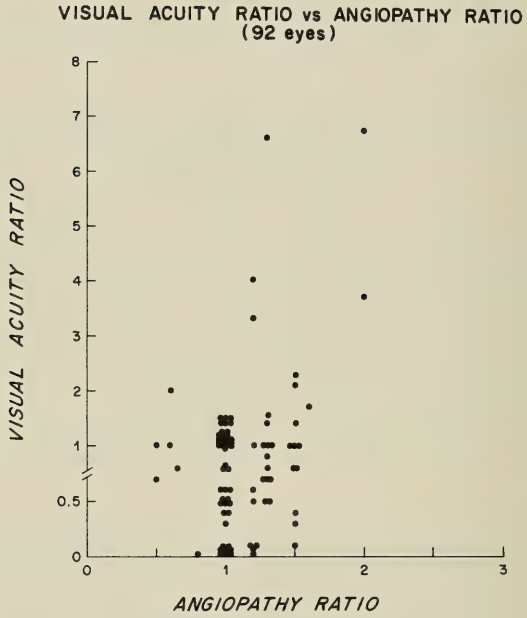
The presence of legal blindness preoperatively (VA $<$ 20/200) but not total blindness (no light perception, VA grade 0.0) provides little aid in selecting patients. In the group who improved, 42 percent were legally blind preoperatively. To improve a small degree from 20/400 may be better than a small improvement from hand movements (VA grade 0.02). However, this eventuality is subject to various opinions from patients and doctors alike. In any event this was ordinarily a factor beyond our control at the time of treatment, and we are here attempting to assess various biologic and clinical effects minimizing the amount of prejudgment influencing the effects. Preservation of

CHART V.—*Average visual acuity ratios—Relation of preoperative angiopathy and proliferation grades in 150 eyes*

O'Hare grade			N_1		N_2			Numbers of eyes		
	Our grade	A_1	A_2	A_3	A_4	A_5	Average	>1.0	=1.0	<1.0
F_0	P_1	1. 00 (1. 0)	0. 25 (0. 0–1. 0)	1. 52 (0. 0–9. 9)	0. 20 (0. 0–0. 7)	0. 30 (0. 0–0. 6)	0. 99	5	6	17
F_1	P_2			0. 68 (0. 0–4. 0)	1. 11 (0. 0–4. 2)	1. 00 (0. 8–1. 2)	0. 85	9	7	32
F_2	P_3			0. 68 (0. 0–1. 8)	0. 65 (0. 0–6. 6)		0. 66	6	6	27
	P_4	1. 00 (1. 0)	1. 00 (1. 0)	0. 88 (0. 0–3. 3)	1. 34 (0. 1–6. 7)	0. 50 (0. 5)	1. 01	7	7	13
	P_5			1. 77 (1. 0–3. 3)	0. 73 (0. 0–1. 0)	0. 50 (0. 5)	1. 06	1	4	3
	Average	1. 00	0. 48	0. 94	0. 84	0. 74	0. 875			
Numbers of eyes	>1. 0	—	—	15	10	3		28	—	—
	=1. 0	3	2	17	7	1		—	30	—
	<1. 0	—	3	42	41	6		—	—	92

NOTE.—Figures in parentheses represent range.

CHART VI



vision in the 20/200 to HM range is probably an asset to the individuals concerned.

Retinal detachment was present in one-third to one-half of eyes in the four groups, the frequency in each of doubtful difference. Cataracts were rarely present in eyes which improved; in arrested or blind eyes they were of 2½ times greater frequency. Rubeosis similarly altered the prognosis unfavorably. Glaucoma appeared to carry the worst relative portent for ultimate blindness but could account for only a fraction of the blind eyes. As expected vitreous hemorrhages were frequent in all four groups and similar in frequency. Legal blindness, cataracts, retinal detachments, and rubeosis were noted more frequently in the left eyes, and the other findings were of essentially equal frequency.

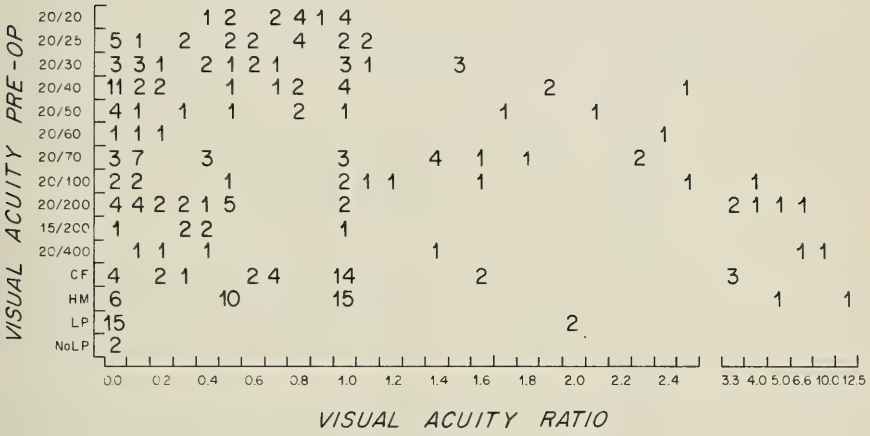
However, each of these factors is of only relative significance in predicting the outcome of treatment and can hardly serve as a confident basis for excluding candidates for therapy.

Causes of Blindness

We studied the material from another point of view: namely, in all those cases totally blind (VA=0.0), what was the distribution of causes. Inevitably, a certain amount of interpretation enters this

CHART VII

VISUAL ACUITY RATIO
vs
PRE-OP VISUAL ACUITY (EYES)



VISUAL ACUITY RATIO ≥ 1.0 and ≥ 0.5
vs
PRE-OP VISUAL ACUITY

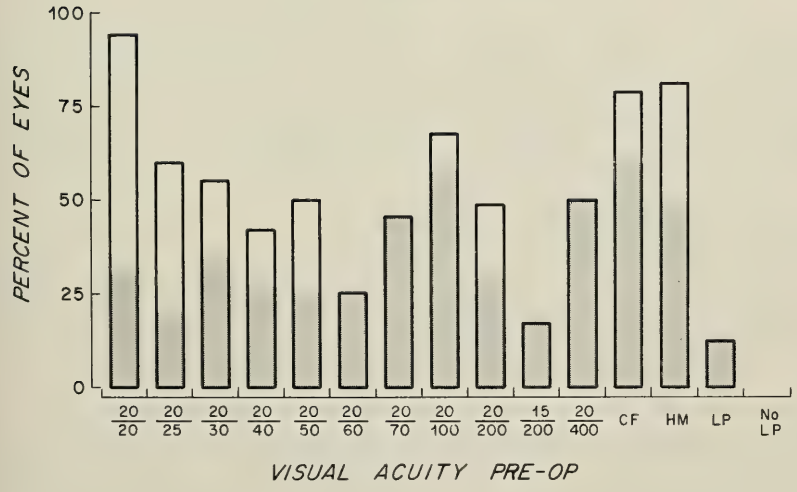


CHART VIII.—*Visual acuity ratio versus summary of other ophthalmologic findings*

	Preoperative VA ≤ 20/200	Retinal detachment	Cataracts	Rubeosis	Exudates	Glaucoma	Vitreous hemorrhages
Improved: VA ratio ≥ 1.1	$\frac{18}{43}$ = 42%	$\frac{17}{43}$ = 40%	$\frac{3}{43}$ = 7%	$\frac{1}{43}$ = 2%	$\frac{41}{42}$ = 98%	$\frac{1}{43}$ = 2%	$\frac{38}{43}$ = 88%
Arrested: VA ratio = 1.0	$\frac{29}{49}$ = 59%	$\frac{26}{49}$ = 53%	$\frac{8}{49}$ = 16%	$\frac{4}{49}$ = 8%	$\frac{44}{49}$ = 90%	$\frac{4}{49}$ = 8%	$\frac{40}{49}$ = 82%
Reduced: VA ratio = 0.1–0.9	$\frac{39}{101}$ = 39%	$\frac{39}{101}$ = 39%	$\frac{25}{101}$ = 25%	$\frac{19}{101}$ = 19%	$\frac{89}{101}$ = 88%	$\frac{16}{101}$ = 16%	$\frac{82}{101}$ = 81%
Blind: VA ratio = 0.0	$\frac{35}{60}$ = 58%	$\frac{22}{60}$ = 37%	$\frac{10}{60}$ = 17%	$\frac{9}{60}$ = 15%	$\frac{54}{60}$ = 90%	$\frac{15}{60}$ = 25%	$\frac{52}{60}$ = 87%

assessment, and single causes cannot be truly isolated. Fifty-three blind eyes presented enough followup data to permit some analysis (chart IX). We attributed the final blindness to the preoperative visual acuity worse than count fingers in over one-third of the blind eyes. New hemorrhages in 10 eyes (19 percent) seemed to be the immediate cause of blindness. Retinal detachment was considered the cause of blindness in eight eyes (15 percent) and glaucoma in six eyes (11 percent). In the remaining 12 eyes we scored the conditions noted most conspicuously—rubeosis, late loss of vision for no obvious reason, exudates in the macula, acute hypertensive encephalopathy, and terminal uremia during the last few days of life.

CHART IX.—*Causes of Total Blindness (53 eyes)*

	Percent
Blind preoperatively (worse than count fingers)	36
New hemorrhages postoperatively	19
Retinal detachment	15
Glaucoma	11
	Eyes
Rubeosis	4
Advanced proliferation (grade 4)	4
Visual acuity loss after 23 months	1
Exudates in macula	1
Hypertensive encephalopathy	1
Terminal uremia	1

Visual Retention Index

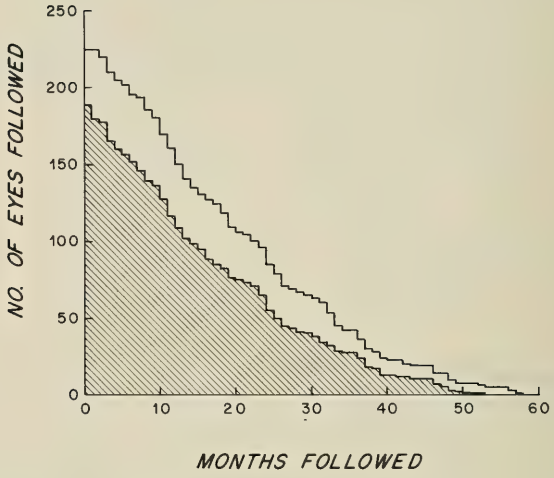
We further analyzed the data from the point of view of the duration of preserved vision by scoring eyes according to a "visual retention index." The visual retention index is defined as the number of months of preserved vision divided by the number of months over which observations were conducted. "Preserved vision" is defined as follows:

Vision ≥20/200	If it remained better than 2 scale units on the standard eye chart below the preop VA.
Vision from 20/400 to HM	If it remained at or above 1 scale below the preop VA.
LP, NLP	If not improved, it was regarded not sustained.

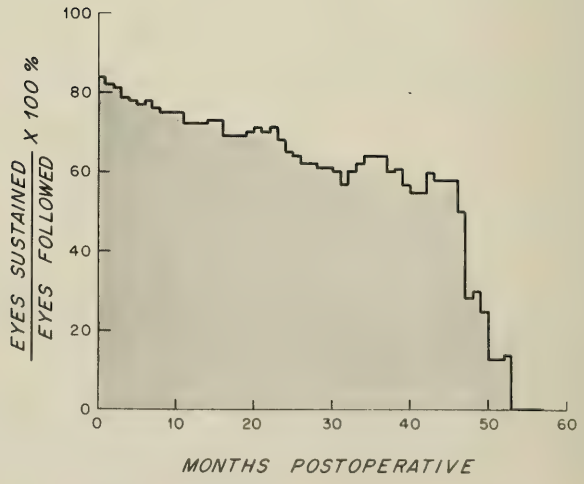
Chart X (upper figure) shows the number of eyes followed in relation to the months of followup and the number of months of preserved vision. The lower figure shows the same data converted to percent of eyes sustained for each followup interval. Initially about 80 percent of patients retain vision which slowly falls over the years to about 60 percent at the 4 year followup. The sharp fall at about 50 months is

CHART X

VISUAL RETENTION
NO. OF EYES
vs
NO. OF MONTHS FOLLOWED
and
NO. OF MONTHS OF PRESERVED VISION



VISUAL RETENTION
PERCENT OF EYES SUSTAINED
vs
NO. OF MONTHS FOLLOWED



mainly due to the small number of patients as the followup duration terminates. We feel it does not represent a sudden deterioration of vision at the 4 year interval.

We studied the factors influencing failure; namely, those eyes with a visual retention index equal to 0.0. We resorted those blind eyes from chart IX according to a visual retention index of 0.0 and excluded eyes in which preoperative ophthalmic examination indicated no promise of vision capable of favorable alteration. In 35 eyes, 9 (26 percent) showed deterioration due to conditions not considered related to pituitary function: retinal detachment (4), glaucoma (2), iritis (1), and unknown (2). Of the 26 eyes with hemorrhages, four proceeded to blindness in spite of evidently satisfactory pituitary suppression. In the remaining 22 hemorrhagic eyes, the inadequacy of the pituitary suppression is accountable for the failure of 63 percent of the blind eyes; five showed no hypopituitarism, 12 were too late in onset of hypopituitarism—1, 2, 2, 3, 3, 3, 4, 4, 5, 5, 6, and 9 months post operative, and 5 were partially hypopituitary.

However, in several instances although an eye failed, the other eye sustained or improved in vision sufficiently that the patient preserved vision. Therefore, the maximum number of patient failures due to inadequate hypopituitarism is 14 or 9.2 percent of the 152 patients followed in this study.

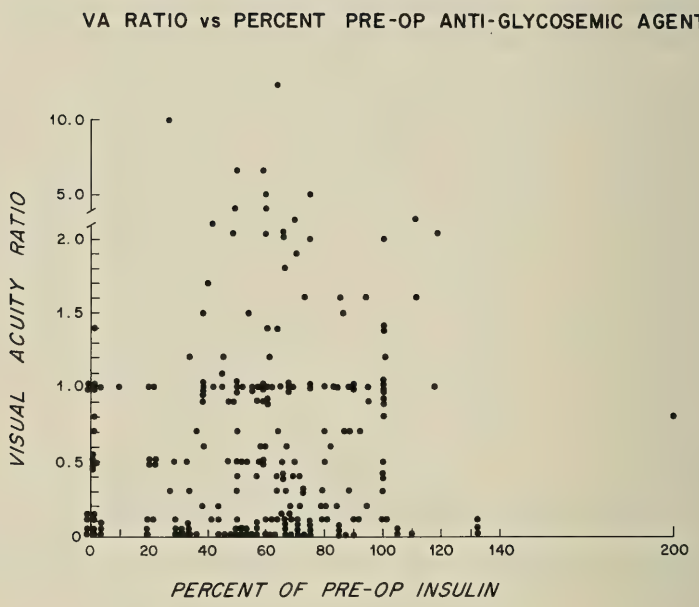
The term "visual retention" as proposed in the O'Hara classification [1] lacks precision in not defining the level at which vision must be preserved. We have defined above the levels we accounted as "retained," considering only values of visual acuity documented by a qualified physician. In reading several of the reports for the Airlie Conference, we are quite unclear about the use of this term by others. It would appear in certain instances that retention of any degree of vision short of total blindness was scored as retained. In others it appears that visual assessment was accounted on the basis of patients' subjective reports without examination by a physician in a majority of the cases reported. The use of "visual retention index" for comparison of a given series or method with another is nearly impossible with the existing variability in its use.

Endocrinology

For reasons stated above, we wish this material was more complete. As a single index of pituitary function, the alteration of requirement for insulin was that available to us in the largest number of patients.

[1] O'Hare Classification, p. XXI.

CHART XI



Protein-bound iodine or other thyroid function tests and menstrual responses were next in availability. Urinary steroid determinations were almost never done and are not considered.

Response of antiglycosemic agents

We elected to correlate the response of the requirement for insulin or other agent to the visual response (VA ratio). In part we have been uncertain to what degree insulin requirement should be depressed to be accounted as an adequate degree of hypopituitarism. Chart XI shows this plot. Of 93 eyes with sustained or improved visual acuity (VA ratio $\geqq$ 1.0), 13 percent showed no fall in requirement for antiglycosemic agent. Of those sustained or improved who did show a fall, the scatter of points appears largely in the range of 40 to 70 percent of their preoperative requirement. A number of patients fell to the 0 to 20 percent range, but many of these lost vision (VA ratio 0.8–0.0).

We have heard proposed that a specific level of fall in insulin requirement such as 50 percent or 25 percent was a prerequisite for a satisfactory ocular response. We are unaware after reading the reports of proponents of this thesis that the contention is supported by specific relevant data. Our data here appear in conflict with this point.

Response of protein-bound iodine test

In chart XII we have computed the alteration postoperatively in this thyroid function test as percent as was done above. Although hypofunction is ordinarily established by this test below a level of normal (3.5μg percent), such a large number of these unfit patients were already below this "normal" as to make the figure not useful. The better responses of visual acuity (VA $\geq$1.0) cluster in the range of 45 to 80 percent of the preoperative value. But again, a number of good visual responses are not related to a fall in PBI, and many examples of depressed PBI are associated with visual loss. The other influences on PBI values are, of course, recognized.

Response of menstrual arrest

This group is naturally more limited in numbers than the previous two groups without sex and age restriction. However, a fairly good correlation exists (chart XIII) in the group showing a good visual response ($\geq$1.0). Nineteen of 21 such women's eyes were associated with arrest of menses. Nevertheless, 16 eyes in women with termination of menses deteriorated to half their previous visual acuity or less.

When we summarized the pituitary function data (chart XIV), we found the relation between arrest or improvement of visual acuity to have no greater 1-to-1 relationship than the individual functions. This would be expected since not all the causes of blindness in these diabetics are due to endocrine-sensitive lesions. Further, the incompleteness of our metabolic data restricts us from using a category which might be called complete hypophysectomy in a conclusively documented sense. We had hoped a review of this material would give an indication of the degree of pituitary suppression or the specific parameters most reliable in promoting arrest or improvement of visual acuity. In general, half the patients showed arrest/improvement of visual acuity in relation to pituitary suppression, and another nearly 10 percent showed a favorable response independent of pituitary suppression. This latter figure compares with the spontaneous arrest

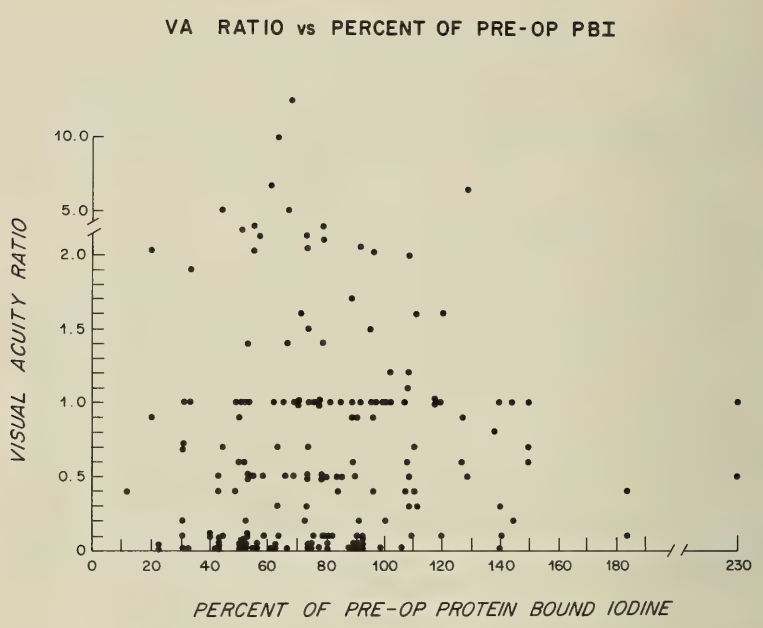


Chart XII

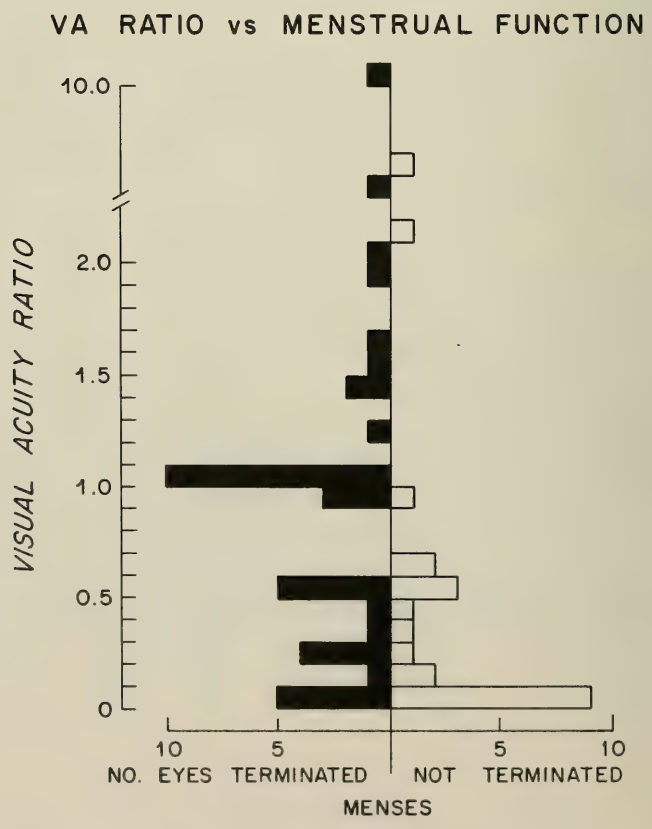


Chart XIII

CHART XIV.—*Visual acuity ratio versus pituitary function (139 eyes)*

	Pituitary suppression	No pituitary suppression
VA ratio ≥1.0 (stable–improved)	$\frac{70}{139}=50\%$	$\frac{12}{139}=9\%$
VA ratio = 0.0 (blind)	$\frac{51}{139}=37\%$	$\frac{6}{139}=4\%$

rate (*4*). A number of borderline cases were excluded (VA ratios 0.1–0.9) in an attempt to show most clearly the relation between hypopituitarism and visual preservation. Although we had hoped that these cases who were eupituitary would serve as a so-called control group, it is not clear that the data warrant such a conclusion.

Mortality

Of the 171 procedures in 166 patients, 37 patients have died. In none of the patients is there any indication that death was related to the stereotaxic procedure. The causes of death are listed in chart XV.

Renal and cardiac disease together accounted for just over half the deaths. All of these patients had their respective causes of death as conditions known preoperatively. The patients dead of nephropathy died 9, 9, 12, 12, 15, 25, 26, 35, 45, and 49 months postoperatively. The

CHART XV.—*Causes of death—37 patients*

Renal	10
Cardiac	9
Stroke	3
Insulin reaction	3
Other (gangrene, ruptured esophageal varices, bleeding gastritis, debilitation, adrenal crisis, aspiration, and aspiration pneumonia)	7
Unknown	5

LIFE TABLE

Interval of followup (months)	0–12	12–24	24–36	36–48	48–60
Patients dead in that year / Patients followed to that year	$\frac{9}{150}=6\%$	$\frac{11}{102}=11\%$	$\frac{8}{70}=11\%$	$\frac{4}{27}=15\%$	$\frac{2}{11}=18\%$
Cumulative percent dead	6%	17%	28%	43%	61%

cardiac deaths occurred 6, 11, 14, 18, 25, 27, 35, 42, and 51 months after the procedure.

Three patients died of cerebrovascular accidents, and the same number died during an insulin reaction as nearly as we could determine. The other causes seem more or less related to the diabetic state, except that esophageal varices and bleeding gastritis have little or no relation. The single instance of adrenal crisis can be attributed to the hypopituitary state. In five instances, the cause of death was unknown.

The lower part of chart XV shows the life table of our cases. It is of interest to compare this table with that reported by Field (*5*). In a sense this provides some comparison between surgically "fit" (Field's cases) and surgically "unfit" cases (ours). The mortality is somewhat higher during the first few years in the "unfit" cases, but the interval of 50 percent mortality is less marked, occurring during the fifth year in our cases and the fifth to seventh year in the followed group of Field's cases.

Morbidity

The majority of patients detect some degree of headache postoperatively, beginning after a few days and ordinarily lasting a few days. Typically, the headache is retroorbital and supraorbital. It is usually relieved by aspirin.

The only specific untoward effect of treatment we have witnessed is a transient disturbance of extraocular motor (EOM) function. EOM disturbance has been noted in 35 instances, 23 percent for the whole series. In the original pattern of direction of the beams of protons, the incidence was about 40 percent. The most recent computer-determined isodose curve, planned to avoid this complication, has reduced this incidence to just under 10 percent. In every case in which EOM disturbance has been followed, it has subsided.

The onset of EOM disturbance averages 3.0 months after treatment, ranging between 2 weeks and 16 months. The average duration of the complaints has been 12.2 months (ranging 2 weeks to 27 months). The complaint of diplopia was registered 21 times and ptosis in 12 instances. Examination showed the third cranial nerve involved in 24 instances, and the fourth and sixth nerves identified in one instance each. Bilateral disturbance was noted twice.

In one patient only, a question of injury to the optic chiasm has been raised. Preoperatively the patient showed VA O.D. 20/50, O.S. C.F. Glaucoma was found bilaterally-tension O.D. 30, O.S. 31, and visual field defects (largely binasal) were attributed to the glaucoma.

Rubeosis was present O.D. 3+ and O.S. 2+. The right macula was described as showing mild edema, microaneurysms, and retinal hemorrhages. Postoperatively the VA O.D. regressed to LP. The fundus showed remission of angiopathy and atrophy of the disk. Although glaucomatous blindness is the likely basis, we know of no way to confirm exclusion of possible radiation injury.

Diabetes insipidus requiring Pitressin has occurred in six instances of 1 to 9 months' duration. Four additional cases were known to have excessive thirst and voiding frequency in which no Pitressin was given.

DISCUSSION

The complexity of the problem of diabetic retinopathy is given testimony by the existence of this conference. Our study has placed some quantitative character upon a number of the ophthalmologic and metabolic factors in relation to the particular procedure we do in the particular patients with whom we work, but these represent a broader spectrum of cases than is commonly reported.

Retinopathy occurs in diabetics usually with a fairly long history of diabetic disease and frequently along with significant diabetic complications in other systems. Even this considered truism has exceptions. A few of our cases were not known to be diabetics prior to their initial ocular symptom, and a few cases required no treatment of their diabetes.

Parallel pathologic processes exist of neovascularization associated with hemorrhages and fibrous proliferation associated with opacification of the vitreous and retinal detachment. The course of the angiopathy is capable of arrest or reversal by pituitary suppression with fairly high reliability, but we have nearly no examples of reversal of proliferative disease. Unfortunately, arrest or regression of angiopathy carries no immunity against further hemorrhages. The normal course of the blindness is variously insidious or apoplectic or occasionally spontaneously arrested. Besides hemorrhages, several other ocular states contribute to blindness, but blindness due to hemorrhage is often related to inadequate pituitary suppression.

The Bragg peak proton method of pituitary suppression has evidently been rewarded by a certain measure of endorsement by the medical community. Most of the conventional procedures reject 50 to 80 percent of the diabetics with ophthalmologic criteria for treatment because of renal, cardiac, or other system disease (*6*, *7*, *8*, *9*, *10*). In

general this rejected group is the one treated in this report. In our experience 50 percent of the patients are alive over 4 years and approach the life expectancy of surgically "fit" diabetics. We strongly urge these patients be considered for sightsaving therapy. About 80 percent are capable of preserving vision (visual retention index) initially, tapering to about 60 percent over 3½ years. The procedure which minimizes physiologic, psychologic, and economic stress has attractiveness to patients and physicians who reflect upon the means by which useful vision may be preserved. Proton treated patients are ambulatory hours after the procedure as compared with days after conventional procedures. They are ordinarily discharged on the second or third postoperative day as compared with 2 or 3 weeks conventionally. Ordinarily, they can return to their occupation the following week. The hospitalization cost averages more than $1,000 below that of many conventional operations. The choice for less drastic therapy is particularly engaging when the mechanisms by which pituitary hypofunction influence the disease are less than certain and the means of selection of candidates for treatment are of relative precision only. One of our colleagues in internal medicine has been sufficiently enamoured by the method of proton hypophysectomy that he has referred to it as "like medical therapy" as distinct from conventional surgery.

We will continue to perform stereotaxic proton hypophysectomy in appropriate candidates. We will continue to seek new knowledge and new methods to improve the treatment. Specifically, a greater depth of understanding of the endocrinologic mechanisms might be achieved by correlation of visual effects with the primary pituitary hormones, growth hormone, adrenocorticotrophic hormone, melanophore-stimulating hormone, and thyroid-stimulating hormone. With other collaborators such studies have been done in our acromegalic and Cushing's disease patients, and the studies could be extended to the diabetics. The expense in time, money, hospital and laboratory resources would be appreciable, however, and it requires serious commitment of followup resources to be undertaken.

Technical factors can also be improved with existing knowledge but require resources. We have begun to use a satisfactory stereotaxic radiofrequency method for hypophysectomy and can compare the relative merit of the immediately induced hypopituitarism against the proton method which takes a variable number of months to develop and has a failure rate in 1 year's time of about 10 percent. In exchange the radiofrequency method will have a higher stress, higher complication rate, and longer and more expensive hospitalization and convalescence.

CONCLUSIONS

(1) Proton hypophysectomy may be done for diabetic retinopathy with no mortality and modest morbidity.

(2) Angiopathy is usually arrested or improved by treatment. Proliferation is almost never improved and may worsen.

(3) Visual worsening may occur due to hemorrhages, retinal detachments, glaucoma, and other causes. In these cases about one-third of the blind patients were so because of causes other than hemorrhages and therefore had no potential to be aided by pituitary suppression. Occasionally, hemorrhages induced blindness in spite of satisfactory pituitary suppression. Therapy failures resulted in total blindness when there was absence of, lateness of, or incompleteness of pituitary suppression in just under 10 percent of the patients we could study.

(4) The proton method is particularly applicable to surgically "unfit" patients (apparently the majority) because of its low stress and prompt recuperation. The life expectancy of these patients is not so much worse than "fit" patients as to warrant disregarding them.

(5) In diabetic retinopathy, engaging opportunity exists to study ophthalmologic and metabolic mechanisms and for the development of clinical and technical methods to alter it.

Acknowledgments

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CHAPTER 24

Metabolic and Ophthalmological Observations Following Heavy Particle Pituitary Suppressive Therapy in Diabetic Retinopathy

JOHN A. LINFOOT, M.D.
JAMES L. BORN, M.D.
JOSEPH F. GARCIA, Ph. D.
EDWARD MANOUGIAN, M.D.
ROBERT KLING, M.D.
CLAUDE Y. CHONG, M.D.
CORNELIUS A. TOBIAS, Ph. D.
RICHARD A. CARLSON, M.D.
JOHN H. LAWRENCE, M.D.

INTRODUCTION

In the past 15 years a variety of methods have been used to produce hypopituitarism in diabetic retinopathy. Although the followup in these patients has extended to thousands of months, diabetologists, ophthalmologists, neurosurgeons, and radiosurgeons continue to be frustrated by the lack of answers to certain key questions. For example, it is quite clear that hypophysectomy will alter the metabolic state in diabetes, such as lowering insulin requirements, growth hormone levels, etc.; but the metabolic pathways by which such changes may modify diabetic retinopathy are not apparent. In looking at the converse there is little evidence that increased pituitary function either initiates or aggravates retinopathy in diabetes. However, microaneurysms and punctate hemorrhages are infrequently observed in hyperadrenocorticism and acromegaly (*1*), and proliferative retinopathy rarely occurs in these conditions. Thus, hypopituitarism has been introduced in the treatment of retinopathy, on the basis of circumstantial evidence reinforced by the observation of improvement in diabetic retinopathy following spontaneous infarction in the pituitary (*2*).

Another area of difficulty in interpreting the influence of any factor on retinopathy is the rather inadequate prognostic data available on the natural course of simple, and even more importantly, proliferative retinopathy. Although most of us who have been involved in treating diabetics for a long period of time are convinced that many patients

Lawrence Radiation Laboratory, University of California, Berkeley, Calif.

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benefit from the induction of hypopituitarism, we lack control observations to establish therapeutic effectiveness beyond all reasonable doubt.

Further difficulty arises in the selection of patients for treatment. Only recently on the basis of past experience have we been able to establish some criteria for the selection of patients. Even here there is not complete agreement. Despite applying such tentative criteria it is impossible to pick consistently a "winner." Thus while it has become clear that patients with advanced renal and cardiovascular complications are not appropriate for therapy, since their life expectancy is extremely short (*3*), it is less clear what retinal criteria are desirable for therapy. Patients with simple retinopathy have a much better visual prognosis than patients with proliferative retinopathy (*4*). Furthermore, by the time a diabetic has developed proliferative retinopathy, he usually has entered a rapidly advancing phase of generalized vascular deterioration and his life expectancy has shortened (*5*).

Finally, if reduction of pituitary function is indeed effective in controlling diabetic retinopathy, how much reduction of pituitary function is required to palliate diabetic retinopathy? Initally, along with other workers in this field, we assumed that only total pituitary ablation was effective in diabetic retinopathy. Accordingly we delivered sufficient amounts of heavy particles to produce complete destruction of the pituitary. A prompt fall in insulin requirements, hypothyroidism, and hypoadrenocorticism resulted in all of these cases within a few weeks to several months. This comparatively rapid onset of hypopituitarism did not seem desirable because of the complexities of medical management and the further observation, both on a clinical and histological basis, of increased radiosensitivity of brain and nerve tissue in patients with underlying vascular disease (*6*). A less rapid onset of hypopituitarism could be expected from a lower irradiation dose to the pituitary because of the known time-dose relationship of heavy particle irradiation (*7*, *8*) and it was accordingly decided that smaller dose levels should be used. Subsequent studies indicated that these lesser amounts of radiation between 11,000 and 15,000 rads were often sufficient to produce surprisingly consistent changes in insulin requirements, but very few patients developed major hypopituitarism requiring replacement therapy with hydrocortisone and thyroid. We were also somewhat surprised to observe that the visual deterioration and stabilization of retinal pathology in these patients were not greatly different from the group of patients receiving ablative amounts. Consequently we believed that reduction in pituitary function might produce the same end result as total ablation. More recent survival, metabolic, and ophthalmological data on these patients will be presented in this report.

RESULTS AND DISCUSSION

Survival in Diabetics After Hypophyseal Suppression

The majority of the 162 patients on whom we have sufficient followup data had proliferative diabetic retinopathy, and, as indicated in figure 1, had a life expectancy which is not greatly different from the group of patients with proliferative retinopathy followed at the Joslin Clinic (*9*). The 48 deaths (table 1) in this series represent nearly one third of the treated patients. This is consistent with the observations of others (*10*, *11*); and as indicated in figures 1 and 2, improvement or stabilization of retinopathy apparently does nothing to increase the duration of survival in the treated groups. It is disturbing that if alter-

CAUSES OF DEATH	
Renal	27
Cardiovascular	17*
Adrenal crisis	2
Hypoglycemia	1
Suicide	1
	Total 48
AGES AT DEATH	
22-29	4
30-39	19
40-64	25

* 1 CVA

TABLE 1.—*Survival data on diabetic patients treated with heavy particles.*

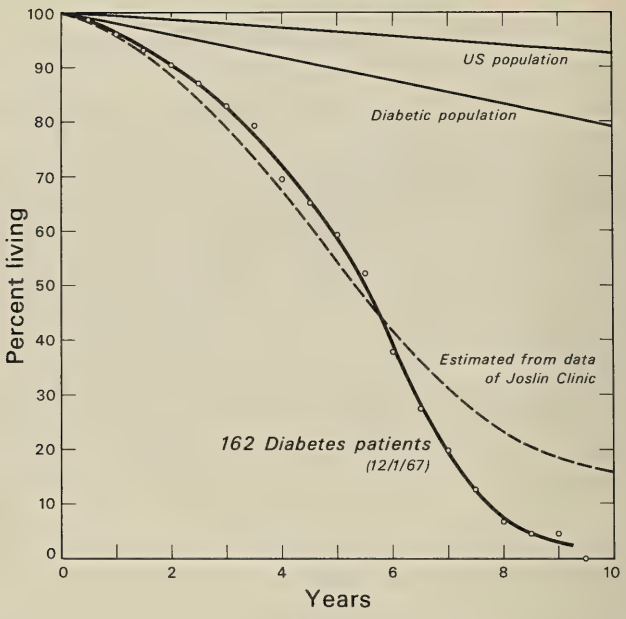

FIGURE 1.—*Survival statistics in 162 diabetic patients with proliferative retinopathy, treated with heavy particle pituitary irradiation. The results are compared to data obtained from untreated patients with proliferative retinopathy followed at the Joslin Clinic.* (9)

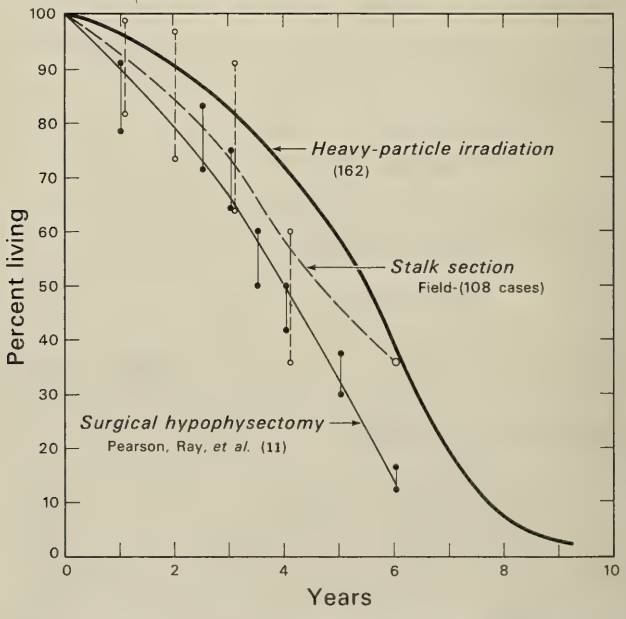

FIGURE 2.—*Similar survival curves are observed when data from patients irradiated with heavy particles, stalk section, and surgical hypophysectomy are compared.*

ing pituitary function, which has such widespread metabolic effects, may influence vascular lesions in the eye it does not apparently effect changes in other tissues such as the kidney, nerves, and large vessels (*8*). Such observations serve as a strong stimulus to a more fundamental approach to an understanding of diabetic retinopathy with the hope that we can develop some form of therapy which, if introduced sufficiently early, may interrupt the progression of generalized vascular lesions in the diabetic.

Materials and Methods

Metabolic studies are reported on a series of 37 diabetic patients 1 to 8 years following pituitary irradiation in the 8,000- to 15,000-rad-dose range. The studies reported were done on all patients admitted to the Donner Pavilion for routine followup between January 1967 and March 1968 (26 juvenile diabetics and 11 adult-type diabetics). Time and other limitations did not permit extending these studies to all 162 patients with diabetic retinopathy who had received pituitary irradiation. It is believed, however, that sufficient significant information is obtained to warrant consideration of the metabolic findings on this subgroup. The only patients excluded were a small number who had terminal renal failure and were felt to be inappropriate for study and, of course, patients who required replacement therapy prior to this study. Seven of the patients in this group had some degree of proteinuria; the remainder were relatively free from major renal change at the time of treatment. The majority of the patients had proliferative retinopathy in one or both eyes, but otherwise satisfied the ophthalmological criteria suggested by Field (*12*).

The average juvenile-type diabetic was 39 years old and had diabetes mellitus for 20 years, whereas the average adult-type diabetic was 51 and had his disease for 14 years. The mean duration of followup was 45 (range 12 to 80) months in the juvenile-type diabetic and 56 (range 17 to 98) months in the adult-type diabetics.

Arginine and insulin tests, growth hormone assays, urinary 20,21-ketols, and protein bound iodines were performed as described previously (*13*, *14*). Retinal evaluations were made of 10 to 12 colored photographs using the O'Hara classification.[1] The visual retention index for each eye was calculated by dividing the months that vision was retained in that eye by the total number of months following therapy.

[1] See O'Hare classification, p. XXI.

Metabolic Changes with Hypophyseal Suppression

The first sensitive direct assay of pituitary hormones that we applied to the study of these patients was the radioimmuno-assay for growth hormone. We initially set up a study to measure growth hormone at various times of the day in our diabetic population with particular interest toward the juvenile-type diabetic who was receiving insulin. Samples were drawn fasting, 2 hours postprandially, and at 4 p.m. in the afternoon. In general, the growth hormone values in these patients showed no recognizable pattern, no relationship to the blood sugar drawn concomitantly, and as a group were not greatly different from the values obtained from a group of untreated diabetics. We, therefore, concluded that basal growth hormone secretion often continued in some of these patients following treatment; but it seemed worthwhile to study and test other aspects of growth hormone secretion, namely arginine and modified insulin tolerance tests. The use of the arginine stimulus circumvented the difficulty in establishing basal glucose levels in the diabetics taking insulin because growth hormone response to arginine infusion is independent of glucose levels in diabetics (*15*). In the adult diabetics both arginine and modified-insulin tests were carried out.

The typical changes in the growth hormone response to modified-insulin tolerance tests and arginine tolerance tests following pituitary irradiation are illustrated in the pilot patient study shown in figure 3. This patient received 17,000 rads of heavy particle irradiation and survived 2 years. At autopsy less than 25 percent destruction of the pituitary was observed by light microscopy. While the illustration shown was not of a diabetic patient, comparable changes in the pituitary would be expected in the diabetic patients receiving similar doses of irradiation. Blunting of growth hormone release was observed 2 months after treatment, and a complete blunting of the response developed between 9 and 16 months. Basal urinary adrenal excretion and protein bound iodide remained unchanged in this patient until 16 months after treatment. The direct assays of growth hormone suggested that the release mechanism occurs rather early and is affected by amounts of heavy particles that are insufficient to produce destruction of pituitary cells. Most of the diabetic retinopathy patients described subsequently received lesser amounts of radiation but similar growth hormone effects were observed.

Figure 4 compares the results of arginine tests in 26 juvenile-type diabetics and 11 adult diabetics to a group of normal subjects and a small group of untreated juvenile diabetics with retinopathy. The blunted responses in the treated juvenile-type diabetics is quite strik-

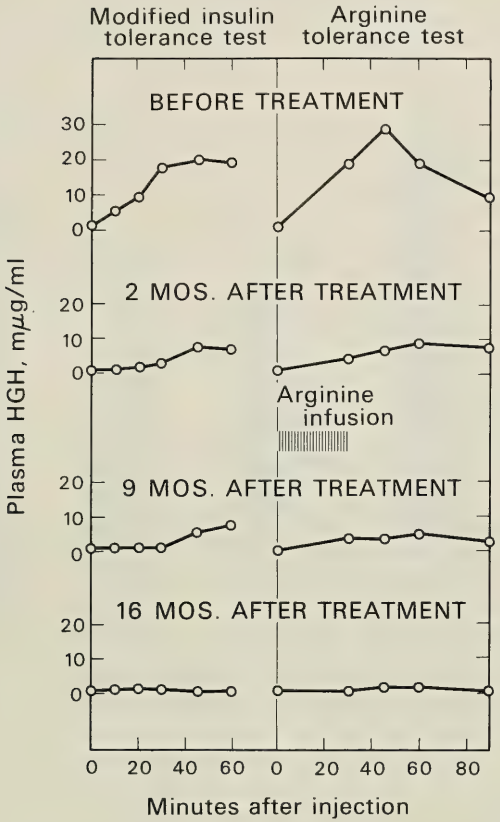

FIGURE 3.—*Typical sequential changes in growth hormone responses in a patient given 17,000 rads of heavy particles.*

ing and greater than that seen in the untreated juvenile diabetics with retinopathy (fig. 4). The response in the adult-type diabetic is difficult to interpret since arginine-induced growth hormone responses are often blunted in untreated adult diabetics (*16*). The growth hormone response to insulin hypoglycemia was also blunted in the adult-type diabetics. Insulin sensitivity, as measured by glucose half life, was increased following treatment (fig. 5).

Figure 6 shows other metabolic changes in these patients. The mean fall in insulin requirements in the juvenile-type diabetic was not due to dietary changes, development of renal failure, or other factors which might influence insulin need. Three patients failed to have any change in their insulin requirements. The change in thyroid and adrenal function was relatively modest; only 13 percent fall in PBI and 18 percent fall in steroid excretion was observed in this group. A 24-percent fall in protein-bound iodide and 35-percent fall in adrenal steroid excretion was observed in the adult diabetics (fig. 5),

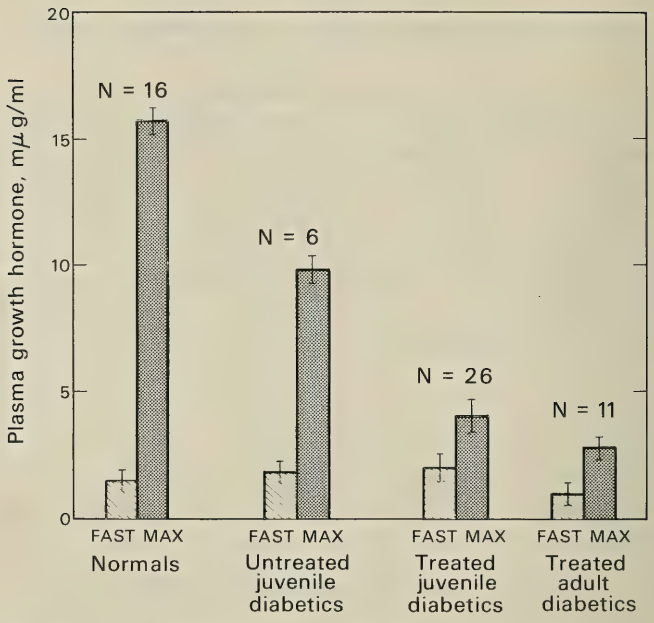

FIGURE 4.—*Fasting and maximal growth hormone responses during arginine provocative (tolerance) tests in normal and diabetic subjects. (Mean ± standard error of the mean).*

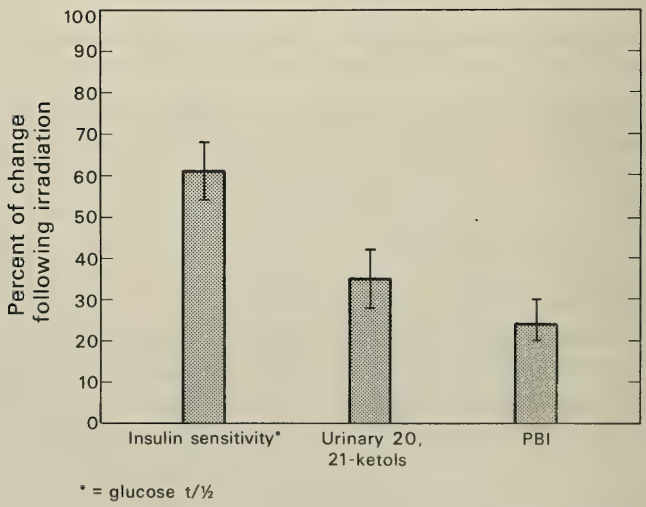

FIGURE 5.—*Metabolic changes in 11 adult-type diabetics. Changes in insulin sensitivity, measured as the difference in glucose t/½, urinary steroid excretion, and PBI were slightly greater than that observed in juvenile-type diabetics. (Mean ± standard error of the mean.)*

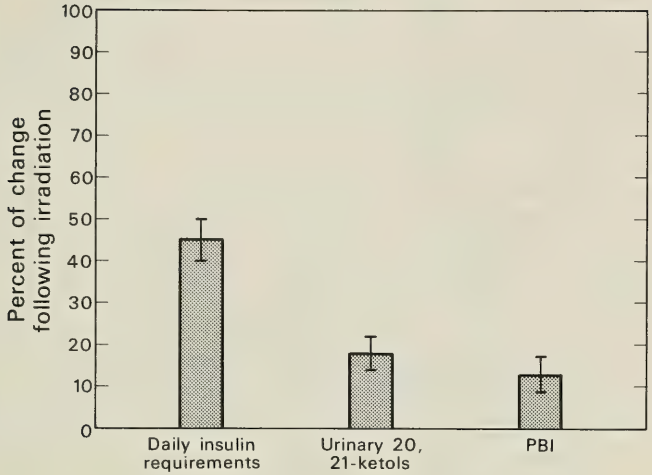

FIGURE 6.—*Metabolic changes observed in 26 juvenile-type diabetics. Percent change in insulin requirements is more striking than that in adrenal steroid excretion (20, 21-ketols) and PBI. (Mean ± standard error of the mean.)*

slightly greater than in the juvenile type. So far four juvenile diabetics have developed sufficient hypopituitarism after treatment to require thyroid and cortisone replacement. Three adult-type diabetics required thyroid replacement. These data show that heavy particle therapy produces a rather consistent fall in insulin requirements and a blunting of the growth hormone response to arginine, with lesser effects on thyroid and adrenal function. Since these studies were performed retrospectively, some reservations in interpretation are necessary and additional prospective studies should be and are being carried out. It is conceivable that there is some abnormality of growth hormone or of pituitary growth hormone release in some diabetics. Although these studies do not establish a relationship between the blunting of the growth hormone response and the change in insulin requirement, it seems reasonable to assume that some change in growth hormone release or some other pituitary hyperglycemic factor is responsible for these observations.

Retinal Changes

In the absence of a control series, a review of the retinopathy in these patients cannot be conclusive, but it may be of some interest to determine the course in these patients. Since the age at onset of retinopathy is a significant prognostic factor (*4*, *5*), we elected to analyze the juvenile-type diabetics separately from the adult-type.

TABLE 2.—*Summary of treated patients*

	Number patients	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptoms	Age at time of treatment	Classification of retinopathy just prior to therapy [1]			Therapy in rads	Duration of follow-up in months	Percent with visual retention index of 1.0 [2] (percent)	Classification of retinopathy at last exam			Degree of pituitary ablation [3]	Complications
					H	N	F				H	N	F		
(*a*) Juvenile-type diabetics [4]	26	19	33	40	0.4	1.1	0.7	12,000	45.4	80	0.4	1.1	1.1	1.2	None
Range		1–44	18–62	18–64				8–13,500	12–80					0–3	
(*b*) Adult-type diabetics [4]	11	37	46	51	0.6	1.4	0.9	12,000	56.0	81	0.3	1.7	1.2	1.1	None
Range		21–54	33–60	34–69					17–98					0–2	

[1] O'Hare classification, p. xxi.
[2] Number months vision retained in at least 1 eye divided by number months of followup.
[3] Pituitary ablation:
0=No change.
1=Change in insulin or HGH only.
2=Replacement with cortisone or thyroid only.
3=Complete replacement.
[4] Mean values.

In the juvenile type 15 of the 26 patients had a visual retention index of 1.0 for each eye at the time of their most recent followup evaluation; or in other words, 51 percent of the patients had maintained the same or better vision in both eyes. An additional six patients retained vision in at least one eye. Thus, 80 percent of the juvenile-type diabetics had retained good vision in one or both eyes at the time of their most recent evaluation. The results in the adult-type diabetics were not greatly different. Five of 11 patients, or 45 percent, had a visual retention index of 1.0 in each eye and an additional four patients, or 36 percent, had retained constant vision in at least one eye. Thus, about 81 percent of these patients currently retain the same or improved vision in one or both eyes.

By using the O'Hare classification of the retinopathy, we found that the retinal pathology showed very little change in either group. The juvenile group showed a decrease in hemorrhages, little or no change in neovascularization, and a slight increase in fibrosis. A similar pattern was observed in the adult-type diabetics.

If the 37 patients were regrouped according to age of onset of diabetes, and patients who developed diabetes under 20 years of age considered juvenile onset patients, and those over 20 adult onset, the following data were obtained: There were 17 juvenile onset diabetics, and 53 percent retained vision in both eyes, and an additional 33 percent retained vision in only one eye; thus, 86 percent of these patients had the same or better vision in one or both eyes at the time of this evaluation. In the 18 adult diabetics only 27 percent retained vision in both eyes, and an additional 44 percent retained vision in only one eye. In other words, 71 percent retained good or better vision in one or both eyes. How significant the difference is between juvenile and adult diabetics is difficult to determine, since the average followup was only 33 months in the juvenile-type diabetics and 52 months in the adult-type diabetics.

From this study we cannot ascertain altered growth hormone secretion to be either a causative or a palliative factor in proliferative diabetic retinopathy. We may simply be observing the natural course of events in these patients. If this is the case, however, the visual prognosis in these patients appears to be somewhat better than we had once thought. Longer followup can only answer these questions. It is clear, however, that some consistent metabolic changes following suppressive doses of heavy particle pituitary irradiation are observed. This therapy is associated with no mortality, little or no morbidity, and may be associated with some benefit on the retinopathy. No effect on the other vascular complications of diabetes has been observed. It stands alone as the only form of pituitary ablative therapy that can

be applied early in the course of diabetic vascular disease, and if it seems necessary and appropriate, a double-blind study can be conducted using this technique. Meanwhile we are still following a contemporary group of untreated patients. In addition we have started a prospective controlled study.

Summary

Heavy particle pituitary therapy with 8,000 to 15,000 rads frequently causes increased insulin sensitivity and consequently decreased insulin requirements in diabetics with retinopathy. Decreased growth hormone response to arginine is also frequently observed. Thyroid and adrenal cortical function appear to be much less affected. These events, however, may not be related to changes in retinopathy. Regardless of the type of diabetes, approximately 80 percent of the diabetics with retinopathy retained constant visual acuity in at least one eye for 3 to 4 years.

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CHAPTER 25

Hypophysectomy for Diabetic Angiopathy: A Controlled Clinical Trial

KNUD LUNDBAEK, M.D.
RICHARD MALMROS, M.D.
HANS CHRESTEN ANDERSEN, M.D.
JENS H. RASMUSSEN, M.D.
ELSE BRUNTSE, M.D.
POUL HENRY MADSEN, M.D.
VIGGO A. JENSEN, M.D.

In 1930 Houssay and Biasotti showed that the diabetic state of pancreatectomized dogs was ameliorated after hypophysectomy. In 1935 Lyall & Innes (*2*) described the Houssay phenomenon in man. A year later Chabanier (*3*) and coworkers published a paper about a young diabetic with pulmonary tuberculosis, in whom hypophysectomy had been performed in order to facilitate insulin treatment. In 1952 Luft (*4*) and coworkers described the first hypophysectomy performed in order to eliminate anterior pituitary factors which they thought might be connected with the development of diabetic angiopathy.

The problem of the value of hypophysectomy in diabetes was accentuated shortly afterwards by Poulsen's (*5*, *6*) publication of his case of diabetic retinopathy receding after the spontaneous development of pituitary insufficiency.

The experiences of the relatively few centers interested in hypophysectomy or other methods of pituitary ablation for diabetic angiopathy have been reviewed recently (*7*, *8*). The impression obtained by most investigators has been that hypophysectomy may produce a certain degree of inhibition of the development of diabetic vascular disease, particularly retinopathy, in certain patients, but the usefulness of this therapeutic measure is still unproved.

The main problems to be solved include the following:

(1) Are the changes observed after hypophysectomy really different from those which may be seen in the spontaneous course of diabetic angiopathy?

(2) Which organs, if any, are benefited by the operation?

(3) To what extent and for how long does hypophysectomy postpone or prevent further development of vascular damage?

From the Second Clinic of Internal Medicine and the Departments of Neurosurgery Otolargyngology and Ophthalmology, Aarhus Kommunehospital, Aarhus, Denmark.

(4) What are the immediate and long-term risks of the various procedures for total or subtotal pituitary ablation?

(5) At what stage of the development of diabetic angiopathy should hypophysectomy be performed?

The following report presents a controlled clinical trial performed in the 5-year period January 1962 to January 1967 in an attempt to answer some of these questions. It must be emphasized, however, that by its very design this experiment can elucidate only some of the problems mentioned above, and also that this communication is a progress report, and will be followed up later, after a longer period of observation.

PLAN OF THE STUDY AND SELECTION OF PATIENTS

Diabetic angiopathy makes its appearance as inconspicuous vascular changes demonstrable by clinical examination such as the presence of a few red dots or mild blurring of the veins in the eye-grounds, diminution of patellar reflexes or (less commonly) traces of protein in the urine. It develops more or less rapidly in the course of 5 to 10 or 20 years, eventually to produce the fullblown picture of totally incapacitating retinopathy, nephropathy, neuropathy, encephalopathy, coronary insufficiency, intermittent claudication and sometimes gangrene.

For a comparative study of treated and untreated patients, it is necessary to study patients defined as closely as possible to one particular stage of this development. This was attempted by adopting the criteria for acceptance to the project shown in table 1. Essentially, they stipulate threatening blindness in the presence of useful visual acuity in younger patients not yet invalidated by kidney or heart disease. As a consequence of these rigid criteria the total number of

TABLE 1.—*Hypophysectomy project, Jan. 1, 1962 to Jan. 1, 1967*

Criteria for acceptance to project:
- Age: <50
- Ophthalmoscopy: proliferations with "gliosis" in at least one eye.
- Visual acuity of best eye: >0.25.
- Serum creatinine: <1.5 milligrams percent, blood urea <50 milligrams percent.
- No cardiac symptoms.

Selection to hypophysectomy or control group:
- At random:
  - Number: 30.
  - Hypox.: 15.
  - Control: 15.

acceptable patients admitted to our departments in the 5-year period was only 30.

After being accepted into the project, patients were selected for hypophysectomy or as controls by a random system.

Narrowness of stage of development and randomization between operated and not operated appears in table 2, which gives the aver-

TABLE 2

	Operated		Controls	
	M (7)	F (8)	M (9)	F (6)
General:				
Age	31	31	33	31
Duration of diabetes (years)	21	21	20	21
Eyes:				
Visual acuity (percent)	62	52	57	57
Heart:				
Blood pressure	143/100	141/94	148/93	137/87
Heart volume (ml.)	476	369	430	400
Kidneys:				
Urine protein (g/L)	0.7	1.3	0.9	1.0
Serum creatinine (mg%)	1.2	1.1	1.2	1.1
Blood urea (mg%)	38	39	42	36
Nervous system:				
Vibration perception threshold	19	17	21	17

age values of some of the essential measurements in men and women of the two groups. It appears that the series should be well suited for a controlled clinical trial.

The patients were studied before operation (or before entering the control group), and every 4 months afterward, during 1 week admissions to the hospital. Attendance appears in table 3. With a few exceptions the patients have cooperated fully in the experimental scheme. Table 3 also shows the examinations performed at each control. Only some of these will be analyzed in this preliminary report.

METHODS

The following analyses were performed in the department of clinical chemistry, Aarhus Kommunehospital: protein bound iodine (*9*), serum cholesterol (*10*), serum creatinine (*11*), blood urea (*12*), urine protein (*13*). Heart volume (*14*, *15*) and vibration sense (*16*) were also determined for each patient.

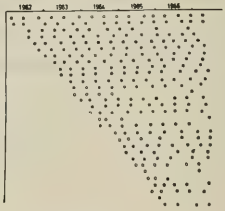
An eye examination using the Zeiss ophthalmoscope, Schepens binocular indirect ophthalmoscope, and slit lamp (Zeiss or Haag Streit 900) with Goldmann's three-mirror contact lens was performed. Extensive verbal description with drawings of all observations was made at each examination with at least five photographs taken of each eye-

TABLE 3.—*Observations.*

OBSERVATIONS

TIME: Before and at 4 month intervals.

EXAMINATIONS: (One week admission).



ENDOCRINE:

Blood & urine sugar, ketone bodies
PBI
BMR
T_3 test
Serum cholesterol, - phospholipid, triglycerides, β LP-cholesterol
17-KS (fractionated)
17-KGS
Gonadotropine

VASCULAR:

Eye examination, complete
Retinal photographs
Biopsy of conjunctiva

Heart x-ray
Ecg

Proteinuria
Sediment examination
Blood urea
Serum creatinine

Legs, x-ray
Skin- and muscle biopsy

Vibration perception threshold (Thesiometry)
Deep reflexes

ground. Visual fields were obtained using Goldmann's projection perimeter, and intraocular tension was determined with the Goldmann applanation tonometer. All eye examinations were performed by two of the ophthalmologists (EB and PHM).

OPERATIVE PROCEDURES AND SUBSTITUTION THERAPY

Transsphenoidal hypophysectomy was performed by the otological surgeon (HCA) and the neurosurgeon (RM) in collaboration, using the technique introduced by Hamberger et al. (*17*). The operation was well tolerated, and most of the patients were able to sit up and take their meals after 1 or 2 days.

Insulin was given postoperatively, according to the results of blood sugar determinations, every 1 to 2 hours for about 1 week, and was later adjusted to the needs of the patients. Administration of prednisone was started before operation and continued afterwards in a dose of 7.5 to (usually) 10 milligrams per day. Full thyroid substitution was instituted later in all patients at the first appearance of signs or symptoms of hypothyroidism. Testosterone isobutyrate, 50 milli-

grams, was given every 2 weeks. Pitressin was needed in the first postoperative weeks or months in all patients.

OPERATIVE COMPLICATIONS AND DEATHS

Transient liquorrhea was noted in two patients. Bacterial meningitis developed in four patients; of these 3 responded quickly to antibiotics, but one died 3 weeks after operation. One of these patients developed a homonymous field defect. One patient developed a transitory oculomotor nerve paralysis.

RESULTS

General Course

One of the control patients developed rapidly progressing cardiac insufficiency, encephalopathy and orthostatic hypotension. She died 1 year after being accepted into the project. One patient got infected superficial gangrene of one foot. It healed without amputation. Ten of the control patients work full time, two are only able to carry out light work. Two patients are on disablement pension for reduced visual capacity. The present condition of the control patients is shown in table 4.

Most of the hypophysectomized patients were able to resume their ordinary work a few months after operation. No cardiac or cerebral accidents have occurred. Small, superficial areas of infected gangrene developed in the feet of two patients, but healed under conservative treatment.

TABLE 4.—*Present condition of control patients*

No.	Years of observation	Occupation	Work
1	5	Farmer	Light work.
2	4	Farmer's wife	Full time.
3	4	Clerk	Do.
4	3½	Housewife	Do.
5	3	Industrial worker	Disablement pension.
6	3	Operator	Full time.
7	3	Industrial worker	Do.
8	2½	Housewife	Light work.
9	2	do	Full time.
10	2	Gardener	Do.
11	1½	Driver	Disablement pension.
12	1½	Industrial worker	Full time.
13	1(½)	Weaver	Disablement pension.[1]
14	1	Housewife	Full time.
15	1	Receptionist	Do.

[1] Died of cardiac insufficiency 1 year after acceptance.

The present condition of the hypophysectomized patients appears from table 5. Two patients have a somewhat reduced working capacity, two others are out of work and on disablement pension, one because of poor eyesight, another (patient No. 14), who was operated a year ago, because of protracted infection in one hand.

Endocrinological Parameters

A few days after hypophysectomy the PBI decreased and reached a new low level in the course of 2 weeks (fig. 1). Mild symptoms or signs of hypothyroidism developed in all patients some weeks later, and disappeared after thyroid substitution.

Variations in the PBI, BMR, and serum cholesterol during the entire period of observation appear in figs. 2, 3, and 4. PBI fluctuates during thyroid medication, but is nearly always in the normal range. Serum cholesterol rises after hypophysectomy, but falls again after thyroid treatment is started. BMR is low despite sufficient substitution. The average decrease in insulin requirement was 39 percent (fig. 5). Menstruation ceased in all hypophysectomized women. No endocrine accidents have occurred in the period of observation.

TABLE 5.—*Present condition of hypophysectomized patients*

No.	Years of observation	Occupation	Work
1	5	Farmer's wife	Full time.
2	5	Weaver	At home.
3	5	Worker	Full time.
4	4	Gardener	Do.
5	3	Farmer	Light work.
6	3½	Shipwright	Disablement pension.
7	3	Housewife	Full time.
8	3	Broker's assistant	Do.
9	3	Housewife	Light work.
10	2½	Farmer's wife	Full time.
11	2	Driver	Do.
12	2	University student	Do.
13	1½	Industrial worker	Do.
14	1	Nurse	Disablement pension.
15	0	Died 3 weeks after operation	

Vascular Parameters

Kidneys

The urine protein values appear from figure 6. There are a few high curves, but no tendency in either direction in any of the groups.

The variations in serum creatinine are shown in figure 7. On the whole there is a tendency to a small initial rise, followed by a small

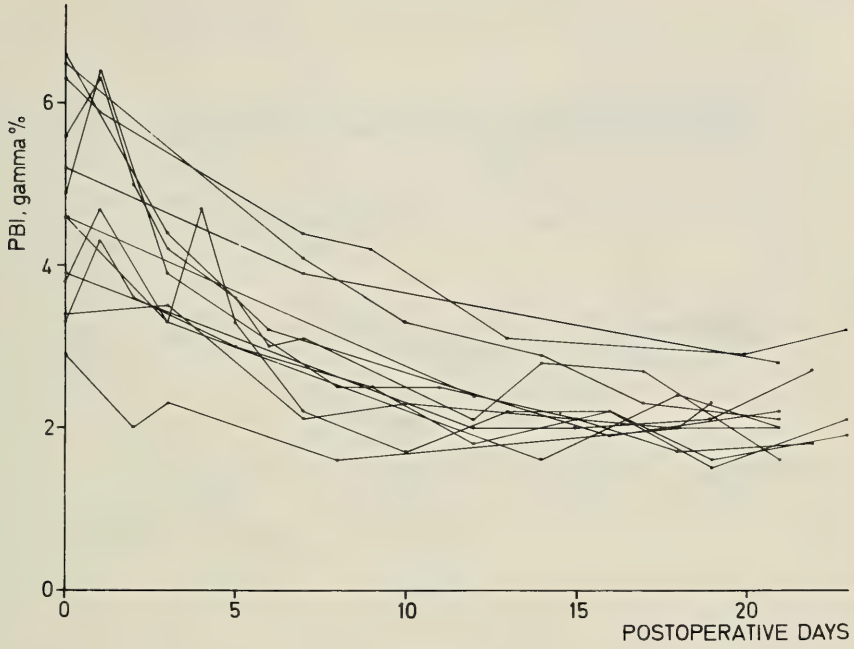
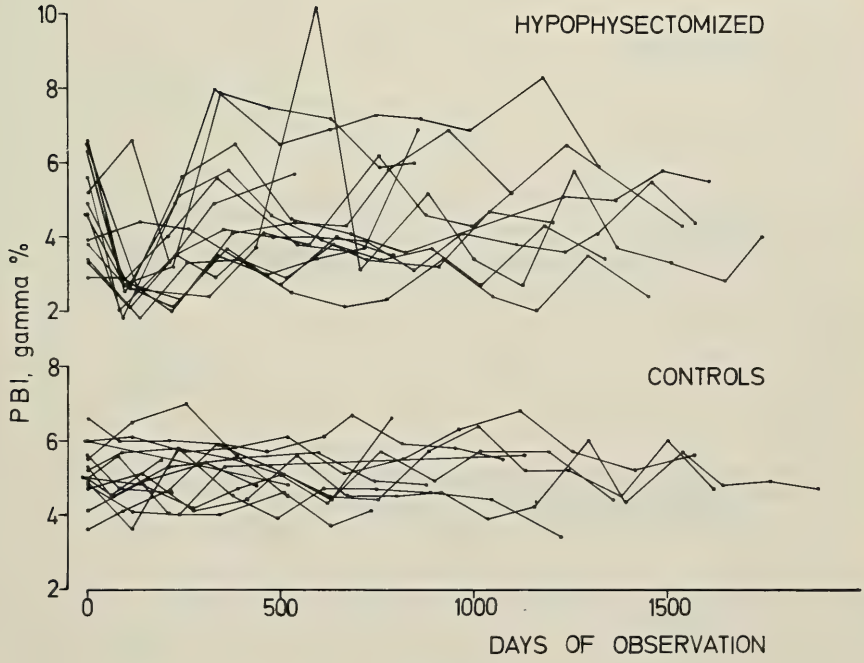


FIGURE 1



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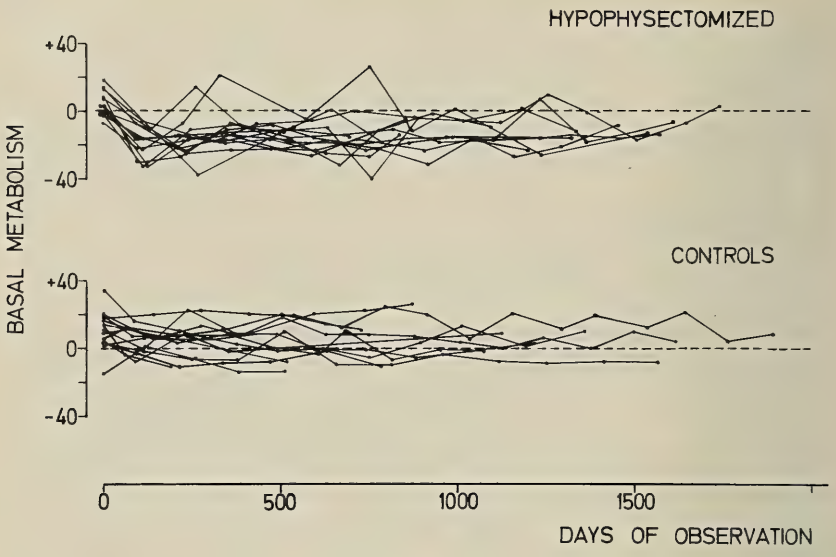

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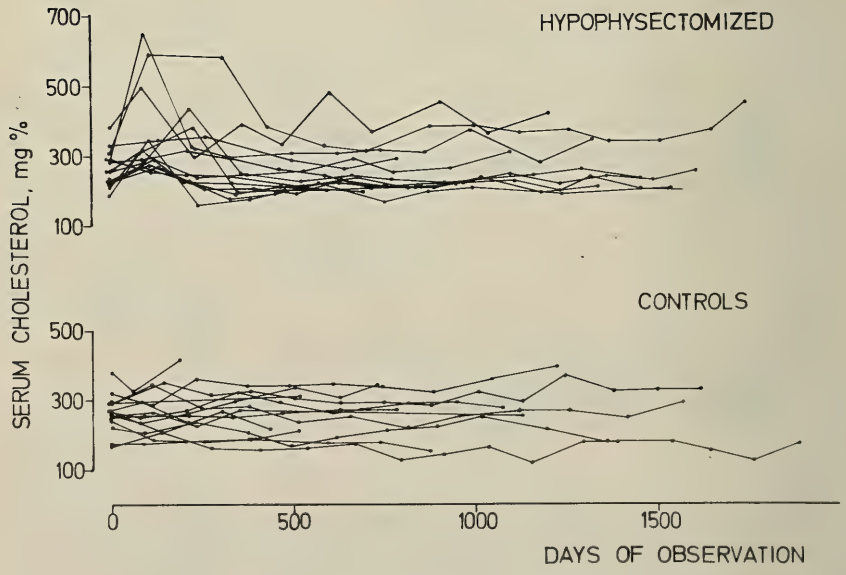


FIGURE 4

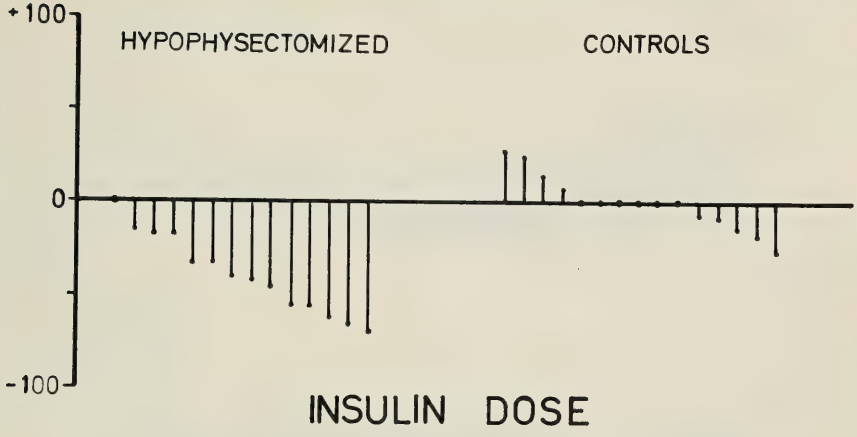


FIGURE 5

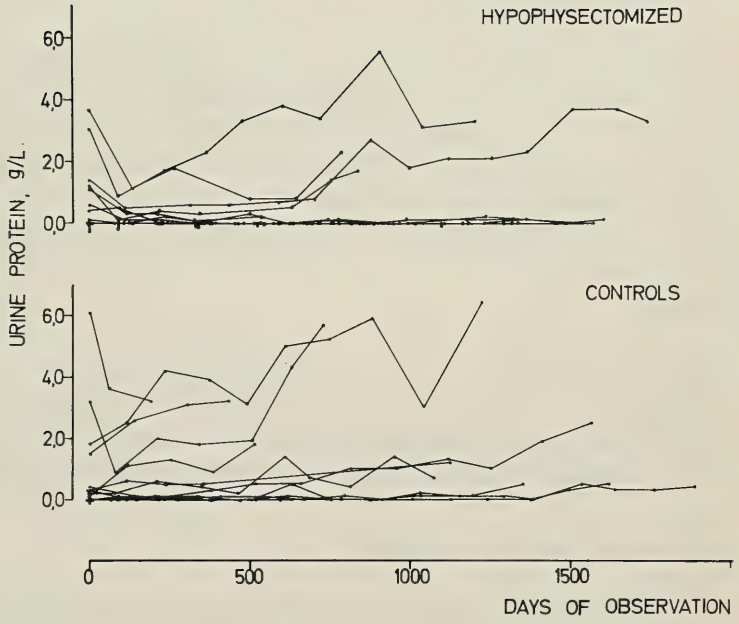


FIGURE 6

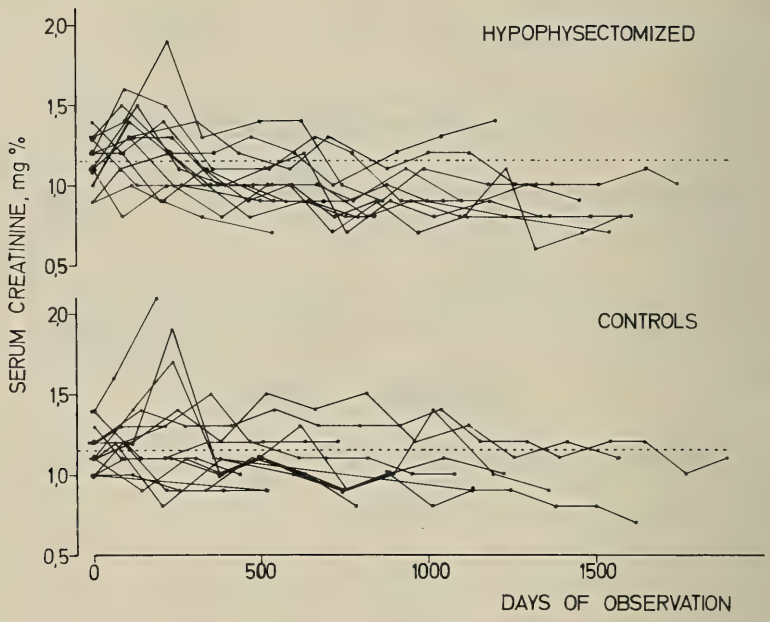


FIGURE 7

decrease in the hypophysectomized group. Most of the decrease seems to occur in the first postoperative months. No change was apparent in the control group.

One of the control patients, observed for only a short time, shows a definite rise. The blood urea is also increasing in this case.

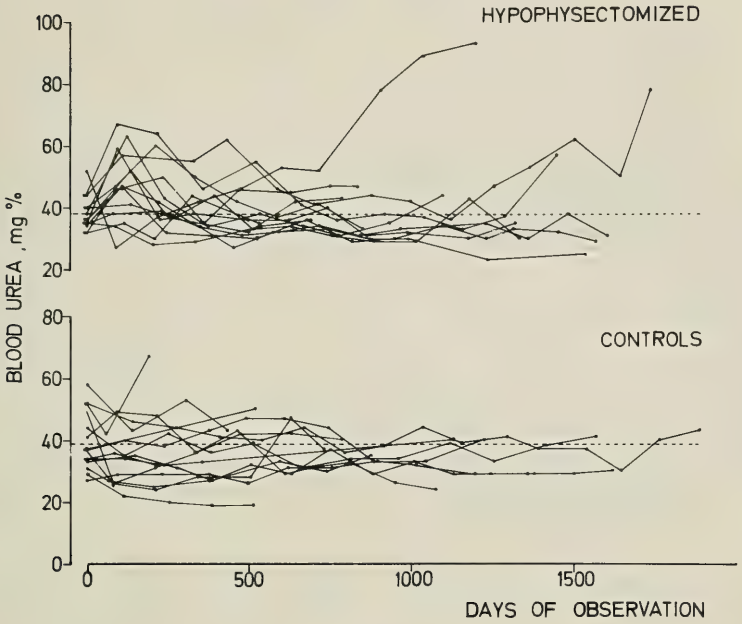
Figure 8 shows the variations in blood urea. A weak downward trend in the hypophysectomized group is apparent here as it also is in the creatinine values. Two patients in the hypophysectomized group show a definite rise, but their serum creatinine is not increasing.

Heart

The systolic blood pressure remained unchanged in both groups (fig. 9), while the diastolic pressure decreased slightly in the hypophysectomized group (fig. 10). The heart volume remained unchanged in the controls as well as in the hypophysectomized patients (fig. 11).

Peripheral nervous system

Vibration sense, measured as vibratory perception threshold, was unchanged in the control group. There is perhaps a tendency to a rise in the group of hypophysectomized patients (fig. 12).



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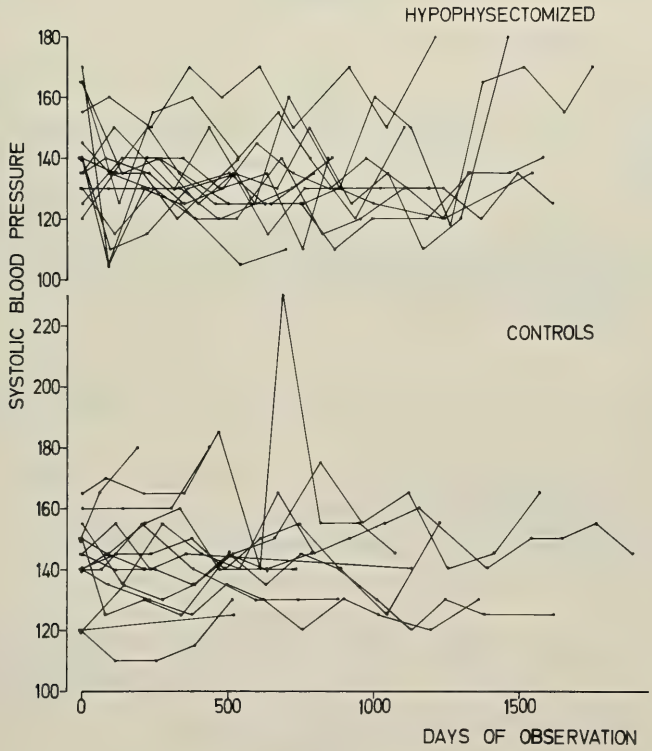


FIGURE 9

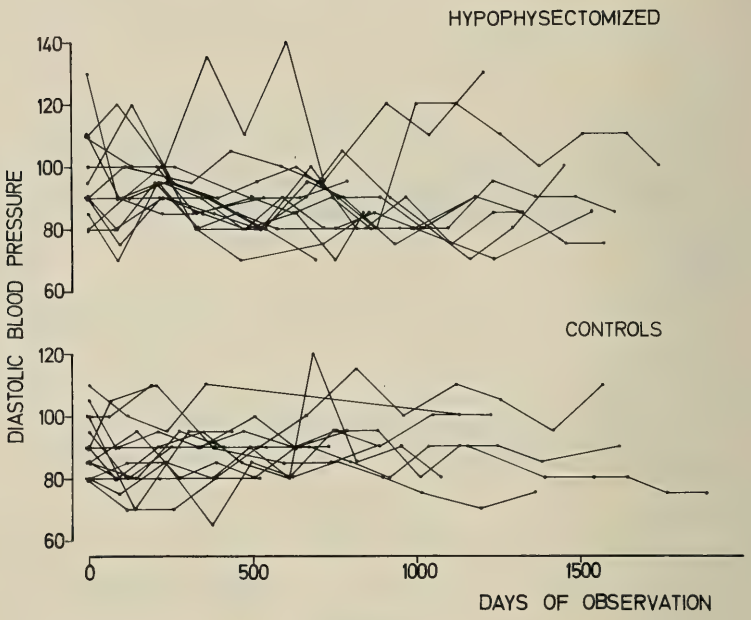


FIGURE 10

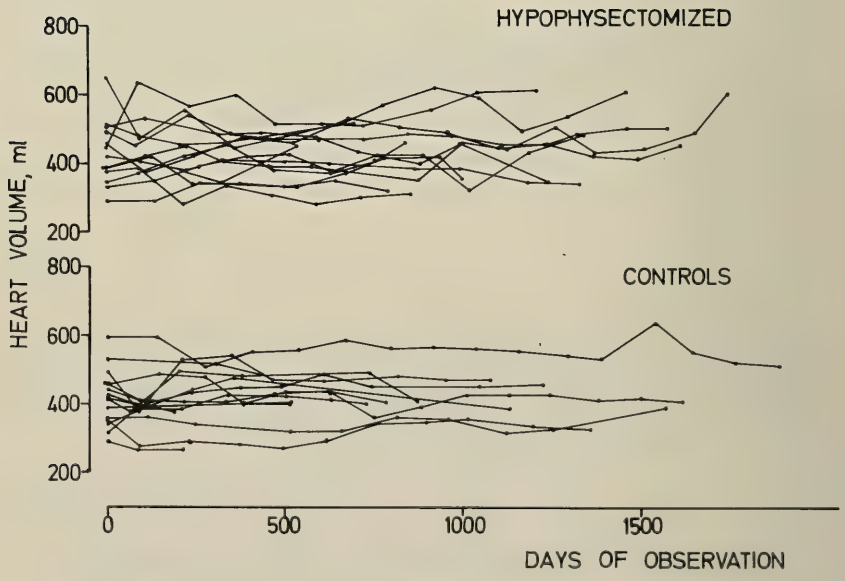


FIGURE 11

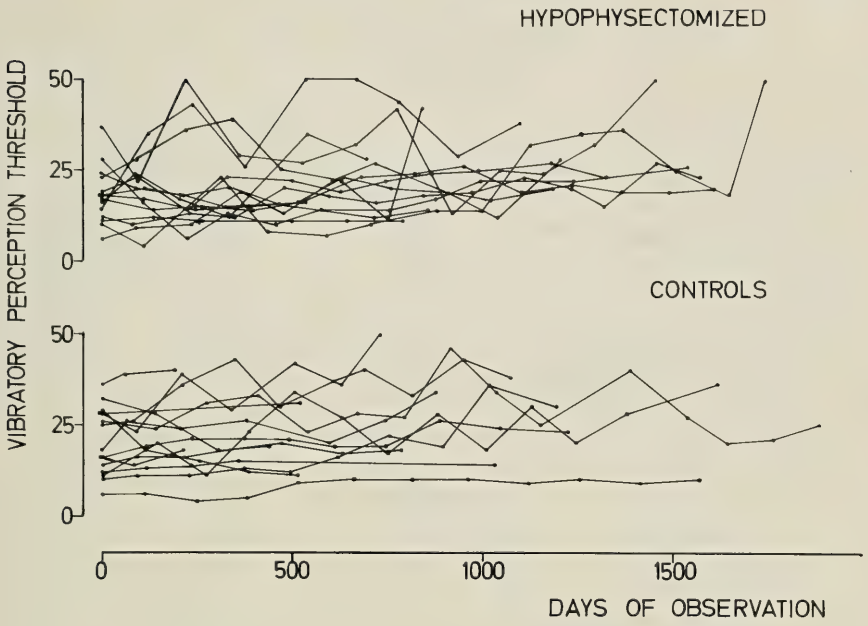


FIGURE 12

Eyes

The distribution of visual acuities in each eye of 14 operated and 15 nonoperated patients at the first and at the last examination appears in figure 13. In the control group the number of eyes with visual acuity of 0.33 or better had dropped from 19 to 11, while in the hypophysectomized group the change was only from 17 to 15.

If only patients with more than 3 years of observation are taken into consideration, the same difference is found. Figure 14 shows that a visual acuity of better than 0.33 was found in 11 eyes at the time of the first examination and in five at the last examination in the control group, while good or reasonably good eyesight was found in eight and seven eyes, respectively, at the time of these two examinations in the hypophysectomized groups.

Figure 15 shows the loss or gain in visual acuity expressed as percentage visual efficiency in the individual eyes in the two groups of patients. Here again the results seem to be different, a preponderance of losses being found only in the control group.

Changes in the visual field (Goldman's projection perimeter) could be ascertained in 17 eyes of the control patients, in 22 of the hypophysectomized group. It appears from figure 16 that the visual field remained unchanged in 35 percent of the controls, as against 56 percent

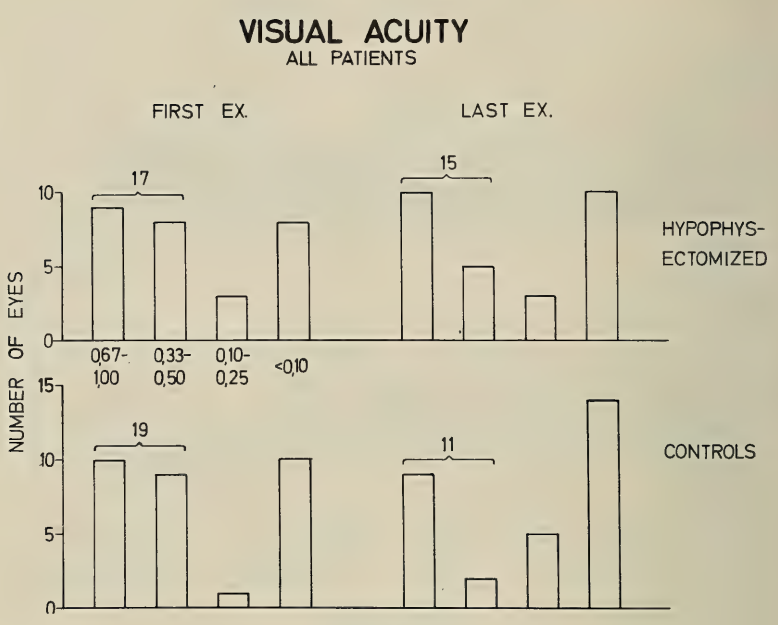


FIGURE 13

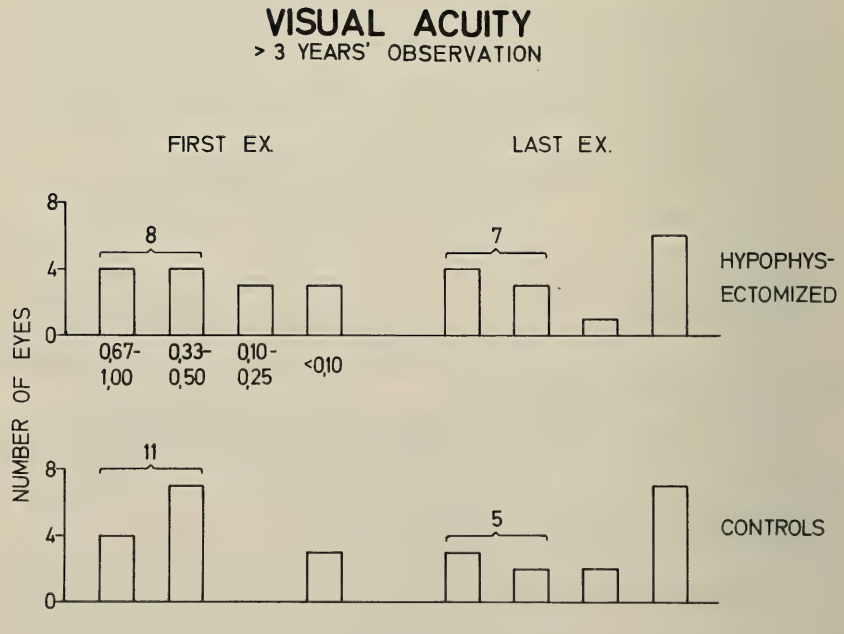
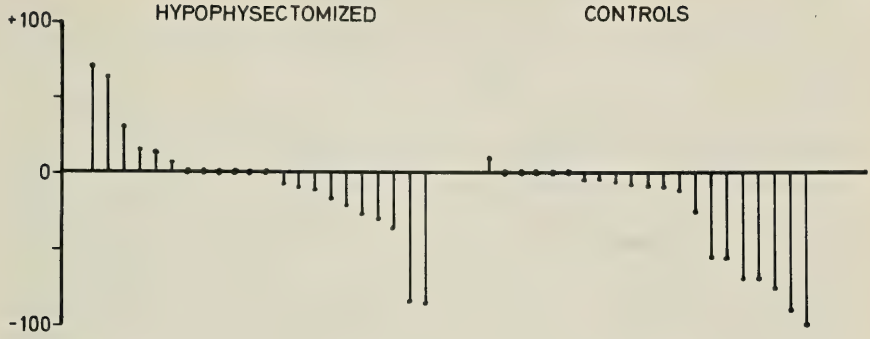


FIGURE 14



VISUAL ACUITY

Loss or gain from first to last observation

FIGURE 15

VISUAL FIELD

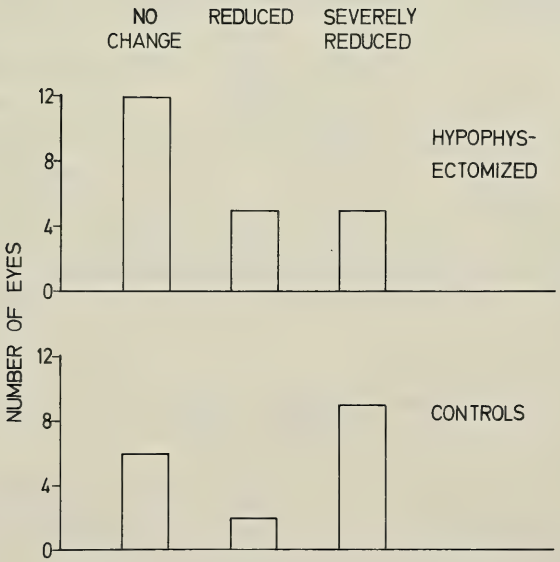


FIGURE 16

of the hypophysectomized patients. Severe reduction occurred in 53 percent of the controls, but only in 23 percent of the hypophysectomized.

The retina was evaluated on the basis of extensive verbal descriptions, drawings, and photographs, as described (see methods).

In many of the operated patients retinal hemorrhages, red dots, phlebopathy and edema diminished immediately after hypophysectomy. These changes seemed rather regular when compared to the spontaneous changes in the control group. However, analyzing the variation occurring in red dots, hemorrhages, phlebopathy and exudates during the entire period of observation, results were obtained as shown in table 6. It appears that no conspicuous difference was observed in these parameters. Periods of regression were often followed by periods of reactivation in both hypophysectomized patients and controls.

The incidence of various degrees of proliferations in the two groups at the first examination is shown in table 7. It appears that early stages of proliferative retinopathy were somewhat more common in the control group than in the group of hypophysectomized patients.

The course of proliferative changes during the experiment appears from figure 17. Progression was seen more commonly in the control than in the hyophysectomized group.

Rubeosis iridis diabetica was present at the first examination in 11 of 30 eyes in the control group and in five of 28 eyes in the group of hypophysectomized patients. It disappeared during the period of

TABLE 6.—*Changes observed in retinal red dots, hemorrhages, phlebopathy, and exudates*

[Number of eyes]

	Controls	Hypophysectomized
Progression	2	0
Regression	8	12
Unchanged	11	5
Very mild changes	2	3
Retina not seen	7	8
Total	30	28

TABLE 7.—*Papillary proliferations*

[Number of eyes]

	Controls	Hypophysectomized
New Vessels	9	4
New vessels plus connective tissue	12	14
None	4	6

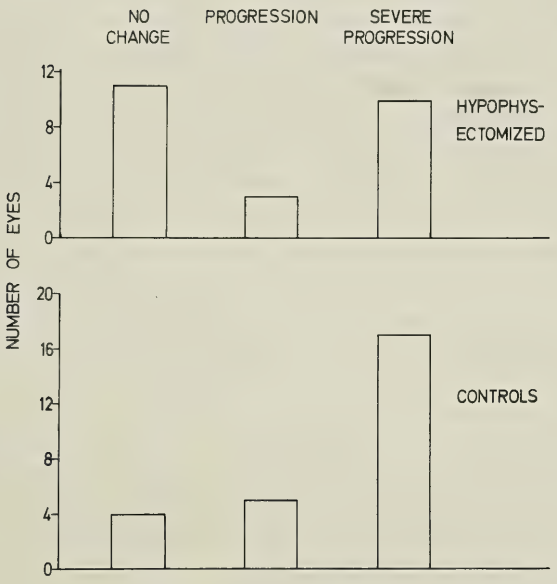


FIGURE 17

observation in three and two eyes, respectively, in the two groups; it increased in six eyes of the control patients, but only in one eye of the hypophysectomized.

Intraocular tension was low in both groups of patients at the first examination (average 11.5 mm. Hg. in the control group, 12.2 in the hypophysectomized group). On the average there was a tendency to a fall to even lower values in both groups during the experiment. However, hemorrhagic glaucoma developed in five eyes in the control group; this complication did not occur in any of the hypophysectomized patients.

DISCUSSION

Transsphenoidal hypophysectomy is not a dangerous operation, but a certain loss is probably unavoidable when it is performed on patients with severe, long-term diabetic manifestations. We have had one death from meningitis in the group of 15 discussed here, and one from postoperative shock among another 19 patients operated earlier.

Except for the development of a field defect in one patient, no permanent sequelae from damage to neighboring structures have appeared. Epilepsy, often encountered after transfrontal hypophysectomy in diabetic patients, has not occurred.

It appears from the result of the present study that hypophysectomy in patients selected as mentioned and substituted as described, affords a certain protection against development of the malignant ocular manifestations of diabetic angiopathy. The so-called background retinopathy (red dots, hemorrhages, exudates and phlebopathy) diminished shortly after operation, but later on it varied considerably in both groups, and no distinctive trend has been observed. However, new vessel formation has developed more slowly in the hypophysectomized group, and visual acuity as well as visual field have been better preserved. It is also interesting that hypophysectomy may protect the patients against progression of rubeosis iridis and the development of hemorrhagic glaucoma.

These results confirm some of the clinical impressions obtained in uncontrolled studies, our own as well as those of other workers (*18*, *19*, *20*, *21*). A recent study on the effect of pituitary implantation of yttrium-90 by Joplin (*8*) and coworkers includes a controlled series of 12, + 11 randomized patients. On the basis of observations on randomized as well as nonrandomized cases the authors conclude that this form of pituitary ablation causes an improvement, not only of new vessel formation, as observed in the present study, but also of hemorrhages and venous dilatation. However, these results are difficult to judge because of the varying degree of hypopituitarism obtained in the individual implanted patients.

The parameters which measure heart and kidney abnormalities in the two groups have not as yet indicated any difference in the development of diabetic nephropathy or cardiopathy between the two groups.

It has been shown repeatedly that glomerular filtration and renal plasma flow are reduced after hypophysectomy in man and animals. Falkheden (*22*) found a fall in the inulin clearance to about two thirds of the initial value in hypophysectomized patients, fully substituted with cortisone, thyroid and sex hormones. Such a decrease from normal initial values would hardly be demonstrable by determination of serum creatinine or blood urea.

In the present study serum creatinine and blood urea were introduced as simple indicators of the appearance of kidney insufficiency. Only three patients, one control and two hypophysectomized, showed changes pointing to an approaching uremic state.

The small overall decrease of serum creatinine and blood urea ob-

served in our hypophysectomized group may be a consequence of hypometabolism.

A tendency to a slowly developing decrease of vibratory sense was observed in the hypophysectomized group, but not in the control group. Subjective symptoms of diabetic neuropathy (paresthesias or night cramps) were present in two of the control patients, in one only at intervals. In the hypophysectomized group paresthesias appeared after 3 to 4 years in two patients, while another patient complained of tingling in the legs on some visits, but not others.

Sexual potency disappeared after hypophysectomy in one man, and decreased in two. Libido decreased in one woman. Sexual activity was low both before and after operation in three patients, normal in seven. In the control group two men and one woman complained of reduced sexual drive and potency.

Orthostatic hypotension: True orthostatic hypotension of the Bradbury-Eggleston (*23*) type with fainting developed in one of the control patients (see General Course), but in none of the hypophysectomized patients.

A fall in blood pressure of more than 30 mm. Hg with a rise in pulse rate but without symptoms was seen occasionally in three of the control patients, and in three of the hypophysectomized. In two of the latter it had been observed before operation.

CONCLUSIONS

We have chosen to study patients with a narrowly defined stage of development of diabetic angiopathy, and to perform pituitary ablation with a method that ensures complete removal of the pituitary gland, in order to limit as far as possible the number of variants in the experiment.

At the present time, with a period of observation of 1 to 5 years, the results of this controlled clinical trial demonstrate a beneficial effect of the procedure on the ocular, but not on any other manifestation of long-term diabetic vascular disease.

By following the trend of events in the years to come we hope to be able to demonstrate more clearly the year by year effect and the final outcome of hypophysectomy on all aspects of diabetic angiopathy.

SUMMARY

A progress report of a controlled clinical trial of hypophysectomy for diabetic angiopathy is presented.

Two well-matched groups of patients, 15 totally hypophysectomized and 15 controls, are studied.

At present (time of observation 1 to 5 years) the ocular manifestations of diabetic angiopathy have developed less markedly in the hypophysectomized than in the control group. No differences have been observed in the renal, cardiac or neurological signs or symptoms, but changes in these have been very slight in both groups.

The study is being continued.

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CHAPTER 26

Hypophyseal Stalk Section as Treatment for Diabetic Retinopathy: Ocular Aspects

J. WALLACE McMEEL, M.D.

The two ocular criteria for selecting a patient to have hypophyseal stalk section have remained constant since 1959. The first is the presence of macular function, as demonstrated by vision better than 20/200 in at least one eye. The second is documentation of progressive angiopathic retinopathy. Every patient treated was examined two or more times to ascertain that the angiopathy was progressing. As exudates and fibrotic avascular proliferation are not affected by pituitary ablation, patients with eyes that had retinopathy primarily of these components did not have this treatment. Also, pituitary ablation was contraindicated for eyes with either early, nonprogressive retinopathy or for advanced changes.

Angiopathy has been the facet of retinopathy that has responded to pituitary ablation. It is comprised of microaneurysms and intraretinal hemorrhages, venous tortuosity, dilatation and segmentation, and neovascularization. Neovascularization is the most significant single parameter in assessing progression of angiopathic retinopathy.

Many patients were found not to be suitable candidates for pituitary ablation. The retinopathy may have been primarily exudative or fibrotic rather than angiopathic or, if angiopathic, either too early for treatment or beyond help.

The decision to perform stalk section was usually made within a few weeks or months after the initial visit. All but a few patients were followed less than 6 months before having stalk section. The above findings suggest that once the critical, progressive phase of retinopathy develops, most patients deteriorate rapidly.

Although macular vision in at least one eye was a prerequisite for hypophyseal stalk section, the fellow eye frequently had a severe loss of vision. Over two-thirds of the patients had vision of counting fingers or less in their worse eyes. Four patients had had one eye enucleated because of intractable secondary glaucoma. The poor status of the fellow eyes indicates that these patients had already experienced significant visual loss due to retinopathy. The patients that had hypophyseal stalk section were most often juvenile diabetics in their early adult life who had already lost vision in one eye and whose remaining eye was rapidly deteriorating.

The effect of the hyopohyseal stalk section on the eyes was rapid. Within a week the turbidity of the vitreous decreased in one third of the cases, usually in those with no significant hemorrhage in the vitreous cavity. After a few weeks the dilated segmented veins appeared less engorged, as did the tufts of neovascularization. If retinal edema had also been present prior to hypophyseal stalk section, is usually cleared. The tempo of increasing frequency of vitreous hemorrhages seemed to abate.

The response of the eyes to treatment was evaluated in two ways. The first was to record the subjective response, the visual acuity, and the other was to note the anatomic changes in the fundus. The visual acuity was assessed by classifying as successful those patients who had maintained vision in either eye equal to the vision at time of stalk section (table I). The other method of determining the course of retinopathy after hypophyseal stalk section was to record the changes in angiopathy and avascular proliferation as noted by ophthalmoscopy. The data in table II applies to individual eyes rather than patients. This is less confusing because in one patient there may be a variable response of the two eyes regarding either neovascular or fibrotic changes. Over 100 eyes were not evaluated because their pretreatment vision of less than 20/200 meant they were not a factor in the decision to perform the hypophyseal stalk section, or because the posttreatment followup was less than 6 months. In the 26 eyes in which angiopathy progressed after hypophyseal stalk section, there was a decrease in vision in seventeen (65 percent). Progressive angiopathy manifested itself most often as recurrent hemorrhage into the vitreous cavity and only infrequently was there extension of areas of neovascularization. Proliferative retinopathy was less frequently halted by hypophyseal stalk section than was angiopathy, as 39 percent of the eyes evaluated had progression of fibrotic proliferation and only 21 percent had progression of angiopathy.

Visual deterioration occurred in 33 eyes despite hypophyseal stalk section (table III). A progressive proliferation or vitreous shrinkage may have been the underlying cause of most instances of decreased vision. Not only are the retinal detachments due to this fibrotic overgrowth and traction, but probably some vitreous hemorrhages were also.

A review of the severity of the retinopathy as graded by the O'Hare Classification [1] reveals that most of the patients in this series were in the most advanced group (N_2 F_2). The success rate, though 68 percent in the 59 cases in the N_2 F_2 classification, was 84 percent in the cases in which the retinopathy had not reached that advanced stage (table IV).

[1] O'Hare Classification, p. XXI.

TABLE I.—*Results of hypophyseal stalk section in the treatment of diabetic retinopathy*

	Number of eyes	Percent
Success	74	72
Regression (visual deterioration after 6 months post-HSS)	17	16
Failure (visual deterioration in less than 6 months post-HSS)	12	12
Total	103	100
Followup less than 6 months	17	
Grand total	120	

TABLE II.—*Status of retinopathy following hypophyseal stalk section*

	Eyes evaluated	Status quo or improved	Percent	Worsened	Percent
Angiopathy	121	95	79	26	21
Fibrotic	117	71	61	46	39

TABLE III.—*Causes of failure regression following hypophyseal stalk section*

	Number of eyes	Percent
Vitreous hemorrhage	15	46
Progressive fibrotic proliferation	7	21
Detached retina:		
Rhegmatogenous	3	9
Secondary	3	9
Rubeosis and glaucoma	2	6
Central retinal artery occlusion	1	3
Unrecorded	2	6
Total	33	

TABLE IV.—*Correlation of results of hypophyseal stalk section with severity of retinopathy (O'Hare classification)*

[S = Success; R = Regression; F = Failure]

	F_0			F_1			F_2		
	S	R	F	S	R	F	S	R	F
N_0	(B_2) 1	—	—	—	—	—	—	—	—
N_1	1	1	—	9	—	1	4	—	2
N_2	1	—	—	10	1	—	40	11	8
Inadequate data to classify							8	2	1

NOTE.—Total: S, 74; R, 17; F, 12.

In the group of sixteen patients that had 20/70 vision or better in both eyes at the time of treatment that were followed over 6 months, fourteen maintained vision, for a success rate of 87.5 percent.

In summary, hypophyseal stalk section has produced an amelioration of retinal angiopathy associated with diabetic retinopathy in over

three-fourths of the eyes evaluated 6 months or longer after treatment. One hundred and three patients were followed for over 6 months, the longest followup being 77 months. Seventy-four patients (72 percent) had maintained their vision at the time of last examination. Of those whose retinopathy had not yet reached the N_2 F_2 (O'Hare classification) stage at the time of treatment, 84 percent were successful. This is significantly greater than the 68-percent-success rate of the N_2 F_2 group.[1]

[1] Determined by a Chi Square test at the 0.05 level of significance.

CHAPTER 27

The Treatment of Diabetic Retinopathy By Pituitary Implanation of Radioactive Yttrium

NIGEL W. OAKLEY, M.D., Ch. B., M.R.C.P.
GRAHAM F. JOPLIN, Ph. D., M.R.C.P.
EVA M. KOHNER, B. Sc., M.B., M.R.C.P.
T. RUSSELL FRASER, M.D., F.R.C.P.

INTRODUCTION

Radioactive yttrium was first used for treatment of diabetic retinopathy at the Hammersmith Hospital 8 years ago. Prior to this time, experience had been gained with the technique in patients with metastatic breast cancer. Over the past 8 years 100 pituitary implants of radioactive yttrium have been carried out for diabetic retinopathy and it is the purpose of this paper to review certain aspects of the results which have been obtained in this series of patients.

In 1965 the same series, which then contained 38 patients, was reviewed in detail (*1*). At this time the implanted series was compared with a randomized control group whose constitution approximated to the patients who had undergone operation. The control group was, however, small, and some of the results, particularly in respect to retinopathy response, were inconclusive. The same series was reviewd again in 1967 (*2*) at which time 60 patients were available. In this second analysis no detailed study was made of the control group, although this was still in progress. Advantage was taken, however, of the varying degrees of pituitary ablation obtained by implantation of radioactive yttrium and the implanted group was divided up according to the degree of endocrine ablation achieved, comparisons being made between groups regarded as having undergone "maximal," "intermediate" and "slight" degrees of ablation. It was felt that by making this comparison a better control situation was being employed, by virtue of the fact that all patients had undergone similar hospitalization and operative intervention. In this second survey, however, three groups of eyes could only be assembled by deriving information from all eyes of all patients treated. Exclusion of unsuitable eyes reduced the available numbers to levels at which no useful statistical comparisons could be made. Thus, although it was concluded that microaneurysms, blot hemorrhages, and new vessels responded to

Department of Medicine, Royal Postgraduate Medical School, London W. 12.

pituitary ablation roughly in proportion to the degree of endocrine deficiency achieved, yet these conclusions were somewhat tentative in that some of the information analyzed was derived from eyes which could not be expected to respond to any known form of treatment. Steady increase in the size of the series and duration of followup has improved this situation, and it has now been possible to analyze the first 100 pituitary implants in terms of the degree of pituitary ablation, using only those eyes regarded as potentially amenable to treatment. The following report outlines the scope of this analysis and presents some illustrations taken from the results so far obtained.

METHOD OF STUDY

The technique of pituitary ablation has already been described in previous publications (*1*). We have continued to use varying radiation doses so that a complete spectrum of endocrine status has been achieved ranging from dependence upon thyroid and adrenal replacement, through to a stage in which a normal growth hormone response to hypoglycemia has been obtained and a normal oxygenic steroid response to metapyrone. For purposes of the present analysis the following definitions have been used:

Maximal ablation: Withdrawal syndrome in 5 days on stopping cortisol replacement; clinically subthyroid with reduced radio-iodine uptake at 3 months after implant; clinical gonadotrophin deficiency; insulin dose in growth-onset diabetes less than 45 percent of preimplant level.

Intermediate ablation: Patients not admissible to maximal or slight groups.

Slight ablation: Normal basal steroid values without withdrawal syndrome on discontinuing replacement; normal thyroid function, clinically and on routine testing; no evidence of gonadotrophin deficiency; insulin dose in growth-onset diabetics within 30 percent of preimplant level.

Retinopathy has been assessed by serial retinal photographs, and estimations of visual acuity carried out preimplant, 3 months postimplant, and subsequently at yearly intervals. The photographs have been graded according to the Hammersmith method (*3*). Using these techniques, separate followup analyses have been undertaken for (1) hemorrhages and microaneurysms, (2) new vessels, (3) venous irregularities, (4) hard exudates, (5) retinitis proliferans, (6) visual acuity. The eyes have been subdivided according to the retinopathy

present at the time of implant. Eyes have been assessed as "irreversible" or "treatable" according to the following definitions:

Irreversible eye: Any eye in which either (*a*) visual acuity is less than 6/24 without reason to believe that this degree of impairment is due to reversible vitreous opacity or definable intercurrent disease unrelated to diabetes and without influence on the retinopathy, or (*b*) retinitis proliferans threatens macular detachment; i.e., if: (1) there is traction retinitis proliferans or well developed traction lines in the internal limiting membrane within 3 disc diameters of the macula, (ii) there is retinitis proliferans secondary to new vessels on the surface of the retina within 3 disc diameters of the macula, (iii) there is retinitis proliferans more than half encircling the posterior pole of the eye.

Treatable eye: Any eye which is not "irreversible," but in which at least two fields are seen to reach grade 2 or more for at least one of the potentially reversible parameters—microaneurysms and hemorrhages, new vessels, venous irregularities. (Eyes showing very severe neovascularization have been subdivided as "florid" but this subclassification need not be considered in the present analysis.) It must be emphasized here that all the analyses set out below relate to eyes rather than patients, the unit being the single eye after one pituitary implant; the complete followup series is thus regarded as 200 eyes even though in fact only 89 patients have been treated, 11 receiving two implants, the principal indication for reimplantation being the persistence of "florid" retinopathy in a patient in whom only "slight" pituitary ablation had been achieved.

The following ophthalmic, endocrine and general features of this series have been collated and subjected to analysis in the present survey:

Ophthalmic followup

Statistical analyses have been made of followup for the six retinopathy parameters mentioned above and also for an overall index of progress. Two groups of eyes have been analyzed: (a) all available eyes, (b) treatable eyes only. Each group has been analyzed both for the 1-year postimplant followup and also for followup to the latest assessment. These ophthalmic followup analyses have been related mainly to the degree of pituitary ablation achieved but correlation has also been sought with initial severity of retinopathy, age and blood pressure.

General medical followup

Serial records of standing and lying blood pressure, tendon reflexes, peripheral pulses, blood urea, plasma proteins, and insulin dosage have all been made and reviewed with respect to the degree of pituitary ablation achieved.

Endocrine followup

Adrenal function has been assessed by withdrawing steroids, given routinely postimplant, at a readmission 3 months after operation. In the event of health being maintained without glucocorticoid supplements, a metyrapone test has been performed to assess pituitary reserve. Thyroid function has been assessed at 3 months postimplant, no replacement being given routinely from the time of operation. Radioiodine uptakes, serum cholesterol estimations and electrographic assessments, together with occasional measurements of protein-bound iodine, have been used to assess thyroid status. In many patients growth hormone has been measured during a hypoglycemic stimulus at 3 months after operation. Records of sex function and menstruation have been maintained, but FSH has not been measured routinely in the patients under study.

General Management Following Pituitary Implantation

All patients have been admitted to hospital for assessment of their diabetes and optimal stabilization prior to operation. Nearly all growth-onset patients have been reestablished on twice daily injections of soluble and NPH (isophane) insulin mixtures, according to the principles described by Oakley, Hill, and Oakley (*4*). This method of treatment has invariably been continued after operation although it is frequently found that morning soluble and evening isophane dose components can be omitted in patients with significantly reduced pituitary function, who are sensitive to insulin and are unable to mobilize glucose in the fasting state (*5*). Steroid cover has been started on the day of operation using high doses of prednisone, reduced rapidly to 7.5 milligrams daily over the first week after operation. This dose is normally maintained until readmission 3 months later when it is withdrawn under hospital supervision to assess endocrine status. Thyroxine 0.3 milligrams daily is started when test and clinical evidence of hypothyroidism has been obtained. Monthly injections of Primotestone-depot, 250 milligrams monthly, are given to male patients complaining of weakness or impotence after operation.

Complications and Morbidity

There have been no deaths in the immediate post operative period. However, in six cases subsequent mortality could perhaps be related to the procedure. One patient succumbed to severe postural hypotension and probable myocardial infarction within 2 months of treatment; one patient died of hypoglycemia after taking a dose of insulin in excess of that prescribed. Two patients died following episodes of meningitis and two patients died in obscure circumstances in which steroid deficiency could possibly have been implicated. Eight patients experienced mild postural hypotension or hyponatremia postoperatively, and there have been eight cases of meningitis, six of which have recovered without incident. Eighteen patients have suffered from some degree of cerebrospinal rhinorrhea, but in only three of these has it been necessary to refer the patient for transantral muscle graft to cure this complication. In five patients the rhinorrhea has successfully been stopped by the insertion of a screw into the anterior wall of the pituitary fossa by an approach similar to that used for the insertion of the yttrium seed, while in the remainder the drip has ceased spontaneously with a short period of bed rest. (With the current implantation technique, the leakage rate is less; reimplantation is feasible when required.) In addition to the six patients already mentioned, 19 other patients have died since operation from causes unrelated to the procedure. In the majority of these cases vascular disease has been responsible; there has been one death from cancer, one for pneumonia, one from renal failure and six patients in whom the exact cause of death has not been established, these being mainly patients referred from abroad who were out of the country at the time of their death or on whom post mortem examinations were not made.

RESULTS

The tables and figures set out below relate only to the 1-year post-implant assessment of treatable eyes. Similar analyses have been made for the total eye population, and both groups have also been analyzed up to their latest followup assessment. Previous experience has suggested that hard exudates and retinitis proliferans are not responsive to pituitary ablation, and these parameters have not been considered in the present analysis. The complete followup information set out according to pituitary ablation grading, and including relevant statistical findings are shown in tables 1 to 4. It will be noticed that exclusion of "irreversible" eyes reduces the number of eyes lost to follow-

TABLE 1.—*Y^{90} implants for diabetic retinopathy—1st 8 years' followup—Ophthalmic Results: grading of hemorrhages and microaneurysms for treatable and florid eyes with respect to 1 year postimplant assessment*

[Total series: 100 implants—200 eyes]

Degree of ablation	Followup in months [1]	No followup because of—		Grading assessments [1]			
		Eye cause	Other cause	Initial (I)		Final (F)	Change from (I) to (F)
All	9.7	6	17	All pts	2.30±0.13 [2](105)	1.51	−0.77
	±0.7			pts c FU	2.28±0.15 (82)	±0.14	±0.09
Maximal (M)	11.1	1	7	All pts	1.84±0.17 (36)	0.85	−0.92
	±1.3			pts c FU	1.78±0.20 (28)	±0.16	±0.14
Intermediate (I)	9.5	4	2	All pts	2.54±0.22 (47)	1.82	−0.71
	±0.8			pts c FU	2.53±0.24 (41)	±0.22	±0.13
Slight (S)	7.9	1	1	All pts	2.53±0.30 (14)	1.93	−0.54
	±1.2			pts c FU	2.47±0.37 (12)	±0.31	±0.23
Nonimplanted controls [3]	([4])			All pts		1.86	−0.24
				pts c FU	2.10±0.14 (41)	±0.11	

[1] Mean ± S.E.M.
[2] Bracketed figures denote the number of eyes in each group.
[3] All eyes.
[4] Approximately 12 months.

STATISTICS

(1) Paired t-tests on initial-final grading changes:
All: p=<0.00001.
Max: p=<0.00001.
Intermediate: p=<0.00001.
Slight: p=0.039.
Controls: p=0.036.
(2) Significance (by t-tests) of intergroup differences, using initial-to-final grading changes from RH column above:
M/I: p=0.27.
I/S: p=0.51.
M/S: p=0.15.
I/C: ———.
M/C: ———.
S/C: ———.
Other: M/I+S: p=0.17.

up by becoming unphotographable or by virtue of photographs not being assessable. This is an important consideration, because such eye losses may easily distort the results of any analysis. It will be seen from results and t-tests set out at the bottom of each table that our present findings strongly support the conclusions of our previous studies—that the dividend obtained in the reversible retinopathy parameters and in visual acuity is proportional to the degree of pituitary ablation achieved, maximum benefit being obtained in patients whose hypophysectomy is virtually complete. Visual representations of the results for hemorrhages and microaneurysms and new vessels are shown in figures 1 and 2. In these figures the initial grade for the parameter displayed is related to the change between the initial and 1-year assessment. A hypothetical "cure line" is drawn upon which would lie

TABLE 2.—*Y^{90} implants for diabetic retinopathy—1st 8 years' followup ophthalmic results; grading of new vessels for treatable and florid eyes with respect to 1 year postimplant assessment*

[Total series: 100 implants—200 eyes]

Degree of ablation	Followup in months [1]	No followup because of—		Grading assessments [1]				
		Eye cause	Other cause	Initial (I)			Final (F)	Change from (I) to (F)
All	9.7	10	17	All pts	1.66±0.11	[2](107)	1.33	−0.36
	±0.7			pts c FU	1.68±0.13	(80)	±0.12	±0.08
Maximal (M)	11.1	2	6	All pts	1.49±0.18	(36)	1.02	−0.66
	±1.3			pts c FU	1.68±0.19	(28)	±0.13	±0.13
Intermediate (I)	9.5	6	2	All pts	1.61±0.18	(48)	1.36	−0.23
	±0.8			pts c FU	1.60±0.19	(40)	±0.19	±0.10
Slight (S)	7.9	2	1	All pts	2.09±0.33	(14)	1.76	−0.06
	±1.2			pts c FU	1.82±0.37	(11)	±0.34	±0.30
Nonimplanted controls [3]	[4]			All pts			0.76	+0.002
				pts c FU	0.76±0.15	(41)	±0.13	

[1] Mean ± S.E.M.
[2] Bracketed figures denote the number of eyes in each group.
[3] All eyes.
[4] Approximately 12 months.

STATISTICS

(1) Paired t-tests on initial-final grading changes:
All: p=0.00003.
Maximal: p=0.00002.
Intermediate: p=0.023.
Slight: p=0.84.
Controls: p=0.98.
(2) Significance (by t-tests) of intergroup differences, using initial-to-final grading changes from RH column above:
M/I: p=0.009.
I/S: p=0.49.
M/S: p=0.04.
I/C: ———.
M/C: ———.
S/C: ———.
Other: M/I+S: p=0.006.

points representing complete remission of the parameter plotted. For hemorrhages and microaneurysms all degrees of ablation seem to benefit the lesions, a finding consistant with that made previously in our last study of this series. It is perhaps unfortunate that, compared with the intermediate ablation group, few maximally ablated patients started with high initial grades of hemorrhages and microaneurysms; no obvious reason can be found for this disparity. For new vessels, the advantage of maximal over intermediate or slight ablation is much clearer, again a finding in line with our previous observations.

An attempt has been made to summarize the ophthalmic findings by devising an index of general ophthalmic response defined as follows:

Good response: Mean grade for microaneurysms or new vessels bet-

TABLE 3.—*Y^{90} implants for diabetic retinoptahy—1st 8 years' followup ophthalmic results: grading of venous irregularities for treatable and florid eyes with respect to 1 year postimplant assessment*

[Total series: 100 implants—200 eyes]

Degree of ablation	Followup in months [1]	No followup because of—		Grading assessments [1]				
		Eye cause	Other cause	Initial (I)			Final (F)	Change from (I) to (F)
All	9.7	15	18	All pts	2.41±0.10 [2]	(110)	2.10	−0.25
	±0.7			pts c FU	2.35±0.12	(77)	±0.11	±0.06
Maximal (M)	11.1	3	7	All pts	2.28±0.18	(37)	1.81	−0.53
	±1.3			pts c FU	2.34±0.19	(27)	±0.14	±0.14
Intermediate (I)	9.5	9	2	All pts	2.25±0.14	(49)	2.06	−0.12
	±0.8			pts c FU	2.19±0.16	(38)	±0.16	±0.07
Slight (S)	7.9	3	1	All pts	2.93±0.27	(15)	2.81	−0.009
	±1.2			pts c FU	2.82±0.30	(11)	±0.28	±0.07
Non-implanted controls [3]	([4])			All pts			1.41	−0.01
				pts c FU	1.42±0.15	(41)	±0.13	

[1] Mean ± S.E.M.
[2] Bracketed figures denote the number of eyes in each group.
[3] All eyes.
[4] Approximately 12 months.

STATISTICS

(1) Paired t-tests on initial-final grading changes:
All: p=0.0002.
Maximal: p=0.0007.
Intermediate: p=0.07.
Slight: p=0.91.
Controls: p=0.91
(2) Significance (by t-tests) of intergroup differences, using initial-to-final grading changes from RH column above:
M/I: p=0.005.
I/S: p=0.37.
M/S: p=0.025.
I/C: ———.
M/C: ———.
S/C: ———.
Other: M/I+S: p=0.001.

ter by 1.0 or more (where possible); and neither worse by 0.5 or more; and visual acuity within one line of initial value or better.

Fair response: Mean grade for microaneurysms and new vessels within +0.4 to −0.9 of initial values and visual acuity within one line of initial value or better.

Poor response: Mean grade for microaneurysms and new vessels worse by more than 0.4 or visual acuity two or more lines worse than initial value.

Using these definitions overall retinopathy response can be related to ablation grade as shown in table 5. There is a clear correlation between response and degree of ablation. The information displayed in figures 1 and 2 is set out in tabular form in table 6. This table shows that the response is unrelated to the severity of the initial grading for microaneurysms and new vessels. The fair response group, in

TABLE 4.—*Y^{90} implants for diabetic retinopathy—1st 8 years' followup ophthalmic results: grading of visual acuity for treatable and florid eyes with respect to 1 year postimplant assessment*

[Total series: 100 implants—200 eyes]

Degree of ablation	Followup in months [1]	No followup because of—		Grading assessments [1]			
		Eye cause	Other cause	Initial (I)		Final (F)	Change from (I) to (F)
All	10.3	0	8	All pts	3.10±0.18 [2](115)	3.38	+0.37
	±0.6			pts c FU	3.01±0.17 (107)	±0.24	±0.23
Maximal (M)	11.3	0	1	All pts	3.26±0.33 (39)	3.03	−0.21
	±1.3			pts c FU	3.24±0.34 (38)	±0.33	±0.36
Intermediate (I)	10.6	0	1	All pts	2.71±0.21 (52)	3.45	+0.71
	±0.7			pts c FU	2.74±0.21 (51)	±0.38	±0.35
Slight (S)	7.4	0	0	All pts	3.07±0.52 (15)	3.60	+0.53
	±1.2			pts c FU	3.07±0.52 (15)	±0.65	±0.60
Nonimplanted controls.[3]	([4])	0	1	All pts		3.90	+0.67
				pts c FU	3.23±0.38 (48)	±0.43	±

[1] Mean±S.E.M.
[2] Bracketed figures denote the number of eyes in each group.
[3] All eyes.
[4] Approximately 12 months.

STATISTICS

(1) Paired t-tests on initial-final grading changes:
All: p=0.11.
Maximal: p=0.56.
Intermediate: p=0.046.
Slight: p=0.39.
Controls: p=0.003.
(2) Significance (by t-tests) of inter-group differences, using initial-to-final grading changes from RH column above:
M/I: p=0.074.
I/S: p=0.71.
M/S: p=0.28.
I/C: ———.
M/C: ———.
S/C: ———.
Other: M/I+S: p=0.069.

which there is little change in the retinopathy, is dominated by patients showing minimal microaneurysms or new vessels—that is very mild retinopathy—at the initial assessment. It is perhaps to be expected that this group would remain relatively static during the 1 year followup period under analysis.

Lastly, retinopathy response has been analyzed in terms of age and blood pressure as it was thought that these might be important considerations in determining the benefit to be derived from hypophysectomy. The results are set out in table 7. It will be seen that there is no obvious distinction between patients above and below the age of 40 and those with diastolic blood pressures above or below a level of 94 mm. Hg. This result was somewhat surprising in view of the clinical impression that older patients and those suffering from hypertension had a poorer prognosis following implant. It is possible,

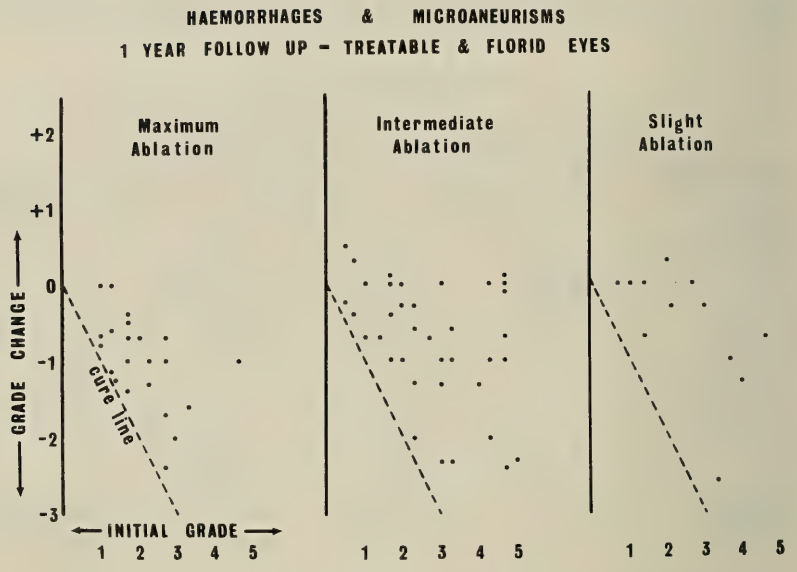

FIGURE 1

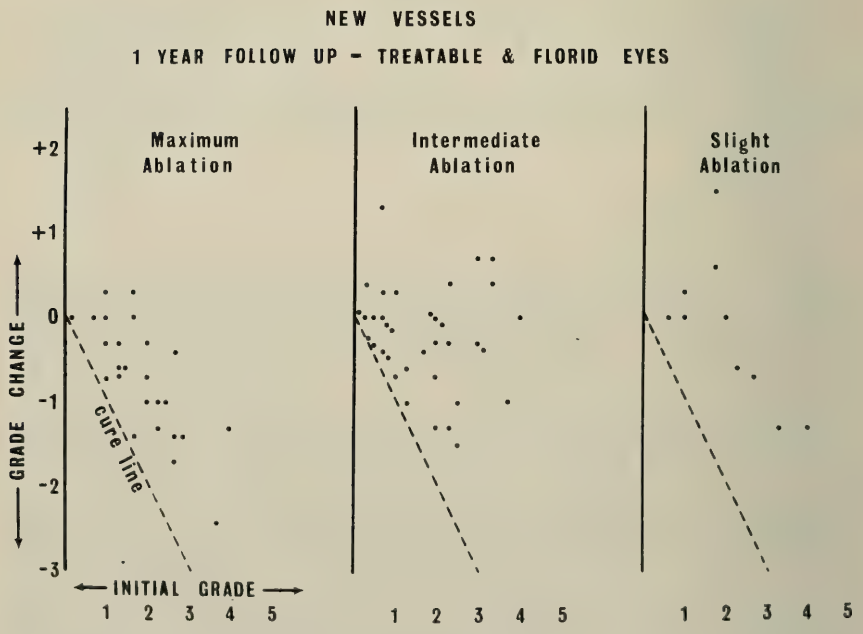

FIGURE 2

TABLE 5.—*"Treatable" eyes—1 year followup—relation of overall retinopathy response to ablation grade*

Ablation grade	Overall retinopathy response		
	Good	Fair	Poor
Maximal	15	8	5
Intermediate	14	15	17
Slight	3	4	6

TABLE 6.—*"Treatable" eyes—1 year followup—relation of retinopathy response to initial severity of microaneurysms and new vessels*

Initial grades		Overall retinopathy response		
Microaneurysms	New vessels	Good	Fair	Poor
0–2	0–2	6	18	9
>2	0–2	9	5	8
0–2	>2	5	2	1
>2	>2	11	1	8

TABLE 7.—*"Treatable" eyes—1 year followup—relation of retinopathy response to age and diastolic blood pressure at time of implant*

Overall retinopathy response		Good	Fair	Poor
Age at implant	<40 years	22	11	16
	>40 years	11	16	12
Diastolic blood pressure	>94 mm. Hg	9	10	12
	<94 mm. Hg	24	17	21

however, that when this analysis is made for the total duration of followup, some support for these clinical impressions may be obtained.

Complete analyses of the results with respect to hard exudates and retinitis proliferans have not yet been completed but it will be very surprising, in view of our previous findings, if these parameters show any response to pituitary ablation. We have previously shown that hard exudates may appear and disappear at random quite independently of endocrine status, while fibrous retinitis proliferans tends to progress regardless of hypophysectomy, although this operation may reduce the appearance rate of new lesions.

General Medical Followup

From the diabetic point of view we have experienced no difficulty in managing patients who have undergone pituitary ablation, and no attempt has been made to maintain the blood sugar levels of these

patients at levels above the desired optimum. There have been very few cases of hypoglycemia requiring hospitalization, the reason probably being that great care has been taken to avoid the use of long-acting insulins, which are particularly dangerous in the hypophysectomized patient.

The general medical criteria for selection have already been reported in our previous publications, and exclusion of patients with blood urea above 75 milligrams per 100 milliliters has almost completely eliminated the problem of renal failure from our followup group. Thus, only one patient has died from diabetic nephropathy while under observation. There has been no evidence of significant improvement or deterioration in renal function during the period of study, and there is no demonstrable difference between the renal status and progress of patients having differing degrees of endocrine deficit. Pituitary ablation may certainly exacerbate mild degrees of postural hypotension, and only diabetics free of this symptom have been considered for implant. In only one patient has hypotension proved troublesome after operation. We have been unable to detect any effect of pituitary ablation on any aspects of diabetic neuropathy.

DISCUSSION

By making comparisons within a fairly large group of patients between those in whom varying degrees of pituitary ablation have been induced, we feel that the best possible type of control situation has been generated. There is no doubt the very fact of being admitted to hospital and undergoing a major operative procedure with possibly far-reaching endocrine consequences will always have a profound effect upon the patient and his attitude towards his underlying diabetes and its management. For this reason no group of patients not subjected to surgery can be regarded as an adequate control group with which to compare patients treated by any method of hypophysectomy. The use of interstitial irradiation enables graded degrees of hypophysectomy to be achieved, and thus, in contrast to surgical techniques, the type of comparison made in the present study can be undertaken. When serial observations of fundal appearances are made on small groups of eyes, there are always problems of heterogeneous retinal status and loss to followup (e.g., due to vitreous hemorrhages). These problems do not arise in following visual acuity; however the latter is only a poor assessment of overall retinopathy and is best considered along with direct observations of the fundal appearances, as has been undertaken in the present study. Many of the criticisms previously levelled

at this type of followup investigation have perhaps been avoided by selection of "treatable" eyes for analysis and exclusion of those regarded as "irreversible" at the time of operation. This type of selection increases the homogeneity of the group and excludes those most likely to drop out from followup during the period of postoperative observation.

It is particularly encouraging that the results of the present study follow so closely those previously obtained in the smaller number of eyes analyzed 2 years ago. It is clear, however, that by no means all patients subjected to hypophysectomy benefit from this procedure and further work must be directed at recognition of those types of retinopathy which are most likely to respond to such a drastic measure as pituitary ablation.

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CHAPTER 28

Pituitary Ablation in the Treatment of Diabetic Retinopathy [1]

O. H. PEARSON, M.D.
C. I. THOMAS, M.D.
B. KAUFMAN, M.D.
C. N. SHEALY, M.D.
W. F. COLLINS, Jr., M.D.
J. JANE, M.D.
C. C. R. JACKSON, M.D.

Since the initial reports of Poulsen (*1*) and Luft and Olivecrona (*2*) that hypopituitarism may induce improvement in patients with diabetic retinopathy, this observation has been confirmed by many other workers. This report presents further experience with pituitary ablation in 52 patients with advanced diabetic retinopathy operated upon in the period from February 1961 to April 1968. We have employed three techniques of pituitary ablation; namely, transfrontal craniotomy, transnasal-transsphenoidal yttrium-^{90} implantation, and sublabial, transnasal, transsphenoidal hypophysectomy in an attempt to delineate the simplest and safest method of accomplishing total hypophysectomy. The long-term results of pituitary ablation on visual retention and on survival in patients with advanced diabetic vascular disease are presented.

PROCEDURES

Techniques of Hypophysectomy

Transfrontal craniotomy was performed in 9 patients and surgical hypophysectomy was accomplished in seven using the technique of Ray (*3*). In two patients pituitary stalk section with the insertion of a polyethylene barrier between the sella turcica and the pituitary stalk was performed because the patients were relatively poor surgical risks.

Transnasal, transsphenoidal implantation of yttrium ^{90} by the technique of Forrest (*4*) was carried out in 32 patients. In brief, this

[1] Data for individual patients in appendix F.

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From the Departments of Medicine, Surgery and Radiology, Case Western Reserve University School of Medicine.

method consists of the insertion of two cylindrical rods of yttrium ^{90}, usually 1 by 3 millimeters in size and of an activity of 5 millicuries each. The yttrium ^{90} rod was encased in a nylon sheath which was firmly fixed to a stainless steel screw. The screw was designed and intended to hold the rod in a predetermined position and hopefully to seal the entry site into the sella turcica to prevent cerebrospinal fluid rhinorrhea. The radiation dosage and placement of the yttrium ^{90} rods were planned to produce tissue necrosis of the contents of the sella turcica.

The patients were anesthetized using a tracheal tube and the head placed in a stereotaxic headholder. Sheathed trocars were inserted through each nostril into the sphenoid sinus under visual control using a portable image amplifier. After appropriate alignment of the trocars, drill holes were made into each side of the floor of the sella turcica, and the yttrium ^{90} rods, attached to the stainless steel screws, were inserted with the use of a screwdriver. All patients received antibotics pre- and post-operatively.

Sublabial, transnasal-transsphenoidal hypophysectomy was carried out in 11 patients using a technique described by Shealy et al. (*5*), which is similar to that of Hardy and Ciric (*6*). In our cases no attempt was made to preserve the posterior pituitary gland. With the use of a binocular microscope and with experience, it was usually possible to accomplish an extracapsular dissection with removal of the pituitary gland in one piece.

Selection of Patients

Patients with severe retinopathy which was threatening blindness were selected for hypophysectomy. Each patient has been categorized according to the O'Hare Classification.[1] Most of the patients had, in addition to background retinopathy, evidence of vitreous hemorrhage, new vessel formation and fibrous proliferation. Eighteen patients had visual acuity of 20/200 or less in both eyes preoperatively. An additional 24 patients had visual acuity of 20/200 or less in one eye preoperatively.

Patients undergoing surgical hypophysectomy were further screened for absence of significant hypertension, coronary disease, severe renal impairment or advanced peripheral vascular disease. Age was not a restrictive factor, however. With the introduction of Y^{90} implant hypophysectomy, patients with more advanced vascular complications of diabetes mellitus were accepted for treatment. Twenty of the 32 patients who underwent Y^{90} pituitary ablation would have been con-

[1] Appendix F and p. XXI.

sidered unsuitable candidates for craniotomy because of vascular disease involving the heart, kidneys, or peripheral blood vessels. The average age in this group of 20 patients was 53 (range 27 to 67). They included three patients with azotemia and creatinine clearances of 30 percent of normal or less, six patients with evidence of coronary heart disease, four patients with moderate hypertension, four patients with advanced peripheral vascular disease, and many with moderate neuropathy.

Although intelligence and reliability were considered important factors in selection, actually only one patient was refused treatment because of unreliability.

There were 28 males and 24 females in this series. The ages of the patients ranged from 20 to 67 years. Twenty-seven patients were 40 years or older with an average of 54 years; 25 patients were less than 40 years with an average of 31 years.

Ophthalmological Evaluation

All patients were examined in the Department of Ophthalmology with measurements of visual acuity, funduscopic examination and fundus photographs obtained before and at intervals after treatment. Evaluation of results was based primarily on comparison of serial fundus photographs, noting changes in microaneurysms, hemorrhages, venous irregularities and new blood vessels, as well as exudates and fibrous tissue. Resolution of retinal edema was best evaluated by funduscopic examination. Patients were considered to be improved if there was maintenance or improvement in visual acuity and resolution of primarily the vascular changes. Patients were listed as failures if visual acuity declined significantly whether there was resolution or progression of vascular abnormalities.

Completeness of Hypophysectomy

An attempt was made to ablate the pituitary gland totally in all cases. Various function tests were carried out pre- and post-operatively in order to assess the degree of pituitary ablation. Thyroid replacement therapy was withheld until chemical evidence of hypothyroidism was documented, usually by measurement of serum protein-bound iodine or thyroidal I^{131} uptake. Rare instances of autonomous thyroid function were documented by failure of thyroid function to suppress following the administration of triiodothyronine. Gonadal function was assessed in premenopausal females by cessation of menses and low

cornification counts in the vaginal smear postoperatively, whereas in males the development of impotence and decrease in size and consistency of the testes were evaluated. Total urinary gonadotrophin excretion was measured in all patients pre- and post-operatively. In the past 2 years, serum luteinizing hormone and follicle stimulating hormone were measured by radioimmunoassay. Serum growth hormone levels were measured by radioimmunoassay during provocative tests such as insulin-induced hypoglycemia and arginine infusion, both pre- and post-operatively. Serum growth hormone levels were usually in the normal range preoperatively and showed a rise during provocative tests. Failure to demonstrate the presence of growth hormone in the serum under similar provocative tests constitutes good evidence for the absence of this hormone. In addition, the insulin requirement was assessed pre- and post-operatively. Following total hypophysectomy the insulin requirement fell to one-third or less of the preoperative level, and this is believed to be due to the withdrawal of growth hormone. (*7*). Failure of the insulin requirement to drop following hypophysectomy constitutes presumptive evidence of incomplete ablation. Adrenal function was assessed in those patients suspected of having incomplete pituitary ablation. These patients were admitted to the hospital, and maintenance cortisone therapy was withdrawn. Plasma and urinary 17-hydroxycorticosteroids were measured daily and the patients carefully observed for development of signs and symptoms of adrenal insufficiency.

In appendix F the degree of incompleteness of hypophysectomy is recorded as a plus sign for each hormone which could be detected postoperatively.

Medical Management

In patients undergoing surgical hypophysectomy insulin dosage was reduced to one-third of the customary amount on the morning of surgery and thereafter adjusted according to urine and blood glucose levels. In the patient with adult-onset diabetes insulin could often be omitted postoperatively. Following Y^{90} implants the decreased requirement for insulin was delayed usually until the fifth postoperative day when an abrupt change occurred. Patients who continued to receive insulin were advised to adjust the dosage by smaller increments than prior to hypophysectomy and to maintain always some spillage of glucose in the urine in order to avoid insulin reactions. Cortisol was administered in large doses to patients undergoing surgical hypophysectomy, and the dose was gradually tapered to a maintenance

level of 37.5 milligrams daily at about 1 week postoperatively. Following Y^{90} implants the patients were started on maintenance cortisone therapy the day after surgery. Patients were warned about the increased requirements for cortisone during intercurrent illness, and all were given identification cards documenting this requirement. Sodium-l-thyroxine, 0.3 milligrams daily, was started at 4 to 6 weeks postoperatively after documentation of hypothyroidism. Patients with a history of coronary heart disease received 0.2 milligrams of sodium-l-thyroxine daily. Male patients received 200 milligrams of testosterone enanthate intramuscularly once a month which was usually started at 4 to 6 weeks postoperatively after documentation of hypogonadism. Young women usually received cyclic estrogen therapy (0.05 to 0.15 milligrams ethinyl estradiol daily for 30 days—then 1 week off) which was started at 2 to 3 months postoperatively when hypogonadism was documented. No significant changes in dietary regimen were instituted after hypophysectomy. All patients undergoing craniotomy received Dilantin therapy for 1 to 2 months postoperatively.

Complications

There was no surgical mortality from the initial therapy in the 52 patients in this series. One patient (not listed in appendix F) died of cardiac arrest during induction of anesthesia in preparation for craniotomy. One patient died of surgical complications during a second Y^{90} implant performed 1 year after the first implant because of incomplete pituitary ablation.

No significant morbidity occurred in the nine patients who underwent transfrontal craniotomy. Of the 11 patients who underwent transsphenoidal surgical hypophysectomy, one had reoperation to replace the cartilagenous graft in the sella turcica because of rhinorrhea. One patient in this group required continued treatment with Pitressin tannate-in-oil for relief of diabetes insipidus.

Morbidity following Y^{90} pituitary implants was more extensive and led to the abandonment of this procedure. Six patients (19 percent) developed rhinorrhea from 1 month to 3 years postoperatively. In five of these patients the rhinorrhea subsided spontaneously, whereas in one patient operative intervention was required to repair the fistula. Two patients developed meningitis at 3 months and at 6 months postimplant. These patients responded to antibiotic therapy and recovered without sequelae. In addition two patients developed febrile illnesses associated with meningeal reaction but with sterile spinal fluids. These patients recovered uneventfully following antibiotic therapy.

One patient developed epistaxis 9 months postimplant which was subsequently shown to be due to intrasellar hemorrhage and required ligation of the internal carotid artery on one side for control of the hemorrhage. This complication was believed to be due to radiation necrosis of the carotid artery (*8*). One patient developed a third nerve palsy at 3 months postimplant which recovered completely within a few weeks. One patient in this group required continuous treatment with pitressin tannate-in-oil for relief of diabetes insipidus.

RESULTS

The data [1] show detailed clinical observations on 52 patients with diabetic retinopathy before and after treatment. Table 1 summarizes our evaluation of the results of treatment on the diabetic retinopathy. Approximately two-thirds of the patients who could be evaluated were considered to be improved as evidenced by visual retention and resolution of the retinopathy. This improvement has been sustained for periods of 1 to 7 years.

Improvement in the ophthalmological findings consisted of resolution of retinal edema, decrease or disappearance of neovascularization, decrease in aneurysms and hemorrhages, decrease in the caliber of blood vessels toward normal, and decrease or disappearance of exudates. The earliest changes consisted of decrease in edema and neovascularization. In a number of patients, extensive neovascularization disappeared within 4 weeks after hypophysectomy, sometimes leaving a thin fibrous band. Fibrous tissue did not regress but remained stable in a number of patients who were classified as improved.

Age was not an important factor in the occurrence of remission following hypophysectomy. Of 30 patients who improved, the ages ranged from 20 to 64 years with a mean of 42 years and a median age of 40 years. Of 16 patients who failed to benefit, the ages ranged from 22 to 66 years with a mean of 42 years and a median age of 39 years.

The classification of the retinopathy at the time of hypophysectomy

TABLE 1.—*Results of hypophysectomy for diabetic retinopathy*

	Number of patients	Percent
Improved	30	58
Failures	16	31
Unevaluated	6	11
Total	52	100

[1] Appendix F.

has prognostic significance. In this series a number of patients with advanced stages of retinopathy were accepted for treatment in order to determine whether any benefit might be obtained. Of 11 patients with retinitis proliferans in both eyes and visual acuity of 20/200 or less in both eyes, seven were considered to be improved on the basis of visual retention or improvement and resolution of vascular changes. Remission has been sustained in this group for periods up to more than 7 years. On the other hand, three patients with bilateral retinitis proliferans and good visual acuity in one eye and who showed resolution of vascular changes following hypophysectomy, nevertheless eventually lost macular vision probably due to contraction of the fibrous scars. Of 18 patients who had visual acuity of 20/200 or less in both eyes prior to pituitary ablation, 10 improved, seven failed to benefit, and one was not evaluated because of short survival. Thus, it appears that some patients with advanced retinopathy may benefit from pituitary ablation.

Completeness of hypophysectomy is considered to be an important factor in insuring optimum results. Of 30 patients who improved, only one had evidence of incomplete pituitary ablation, and in this patient only one hormonal function persisted (thyroid). There were five incomplete hypophysectomies among the 16 failures. The findings in one patient are of particular interest. This patient had a grossly incomplete hypophysectomy and in the ensuing 6 months there was steady progression of the retinopathy. Following reoperation, pituitary ablation was nearly complete (only urinary gonadotrophin was measurable), and there was a striking resolution of the vascular changes. Although this patient subsequently lost macular vision, this is believed to be due to contraction of fibrous tissue rather than an active retinopathy. On the other hand, total pituitary ablation does not insure a remission. There were four patients in our failure group who had complete ablation of the pituitary and a favorable classification of retinopathy who have continued to show active, progressive retinopathy.

Survival following hypophysectomy appears to be related to the extent of other vascular disease. Twenty-two of the 52 patients in our series are dead. Eighteen died of causes related to diabetes mellitus (nine heart disease, three uremia, one stroke, and five infections). Four patients died of unrelated causes (one operative death, one suicide, one cerebral hemorrhage from a berry aneurysm, and one probable hypoglycemia). Four patients in this series had azotemia and creatinine clearances of 30 percent or less of normal preoperatively. Survival in these patients was from 8 months to 3 years. Although the majority of the patients in this series have shown evidence of renal vascular disease, there has been no evidence to date of progressive impairment of renal function.

333-611 O—69——24

DISCUSSION

The observations presented indicate that pituitary ablation can induce significant resolution of diabetic retinopathy in a high percentage of patients. Age does not appear to be an important factor in the incidence of remissions. It has been shown that patients with advanced retinopathy may obtain benefit from pituitary ablation, although the prognosis is much better if advanced fibrosis of the retina is absent.

Experience has been gained with three methods of pituitary ablation. Although transfrontal craniotomy is a satisfactory procedure, careful selection of patients is necessary in order to minimize surgical mortality. Experience with Y^{90} pituitary implantation in 32 diabetic patients, as well as in a larger series of patients with breast cancer, has demonstrated a high incidence of morbidity, and for this reason the procedure has been abandoned. Surgical transsphenoidal hypophysectomy in 11 diabetic patients and in a larger series of cancer patients appears to us to afford the optimum approach for minimizing mortality and morbidity and insuring total removal of the pituitary gland.

This study has not included a series of untreated control subjects because of the advanced stages of retinopathy presented for consideration of treatment. Randomized control studies of patients in earlier phases of the disease are being carried out by others (*9*, *10*), and preliminary results indicate a favorable effect of hypophysectomy. Spontaneous remissions of active advanced retinopathy are rare (*11*, *12*).

The mechanism by which hypophysectomy induces improvement in diabetic vascular disease is unknown. Of the various known pituitary hormones, growth hormone would seem most likely to be implicated, since removal of this hormone is probably responsible for the amelioration of the diabetic state after hypophysectomy (*7*).

SUMMARY

The results of hypophysectomy in 52 patients with advanced diabetic retinopathy have been presented. Two-thirds of the patients evaluated showed resolution of the retinal vascular abnormalities with retention or improvement of vision for periods up to 7 years. Experience with three methods of pituitary ablation suggests that surgical transsphenoidal hypophysectomy affords the optimum approach for accomplishing total removal of the gland with minimal mortality and morbidity.

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CHAPTER 29

Cryohypophysectomy and Diabetic Retinopathy[1]

NATHAN H. ROTH, M.D.
ROBERT W. RAND, M.D., Ph. D.
DONALD A. ADAMS, M.D.
GUNNAR HEUSER, M.D.
ALFRED M. DASHE, M.D.
JOHN HANLEY, M.D.
JOAN GOLD

Pituitary ablation in the treatment of diabetic retinopathy was initially explored by Luft, Olivecrona, and associates (*1*). The rationale for this form of therapy was based on the observation of Poulsen (*2*) of the permanent cessation of hemorrhagic retinopathy in a young diabetic woman following a spontaneous postpartum pituitary infarction. Post mortem examination performed 15 years later demonstrated total anterior pituitary destruction and no evidence of diabetic retinopathy (*3*). Hypophysectomy for progressive diabetic retinopathy has now been evaluated extensively in several centers using various ablative methods. The general impression has been that the retinopathy is inhibited in some but not in all patients.

Extirpative hypophysectomy by transcranial (*4*, *5*) or transsphenoidal (*6*, *7*) approaches produces immediate and usually total hypopituitarism but may be associated with numerous complications and imposes considerable acute stress from a major surgical procedure. Hypophyseal stalk section (*8*, *9*) is not technically as difficult as hypophysectomy and the previous high incidence of resumption of pituitary function is not common if a mechanical barrier to reassociation of the severed fibers is interposed. Transcutaneous radiation (*10*) with heavy particles such as proton beams has the disadvantage of a delayed lag phase from the start of exposure to the decline of pituitary function and unavoidable radiation exposure to adjacent neural structures. Transsphenoidal (yttrium-90) implantation (*11*, *12*, *13*) is well tolerated, but the incidence of delayed complications is high, including extraocular and ocular palsies, cerebrospinal rhinorrhea and meningitis in up to 40 percent of the patients. This technique was abandoned by us because of the high incidence of complications (15 percent) and the difficulty in medical management. Apparently

[1] Data for individual patients are in appendix G.

From the Departments of Ophthalmology (Jules Stein Eye Institute), Surgery (Division of Neurosurgery), Medicine, and Psychiatry, UCLA School of Medicine, Los Angeles, Calif.

there is a delayed necrosis of the sellar floor secondary to the radiation which allows cerebrospinal rhinorrhea to develop.

Stereotaxic transsphenoidal thermal procedures using radiofrequency heat coagulation (*14*) or cryosurgery are effective in pituitary ablation. This report describes our experience since 1963 in cryosurgical destruction of the pituitary gland for diabetic retinopathy.

METHODS AND MATERIALS

We have evaluated approximately 200 patients with diabetic retinopathy for cryohypophysectomy over the past 5 years. Thirty-one patients were felt to be suitable candidates and chose to undergo the procedure. One patient refused surgery. Most of the remaining ones have been unsuitable candidates due to far advanced retinopathy with macular destruction. Some patients with early retinopathy were considered to be future candidates and are still being followed by comparative retinal drawings and ocular fundus photography. Complete postoperative data are not available on patients most recently undergoing surgery.

Ophthalmological evaluation

Patients are referred first for ophthalmological evaluation. A careful history is taken with reference to onset of visual symptoms in each eye, incidence of hemorrhaging into the vitreous and length of time for clearing of the vitreous. An extensive eye examination is performed with emphasis on indirect ophthalmoscopy and contact lens examination. Retinal drawings and fundus photographs are made for comparison at future examinations.

Field's criteria (*15*, *16*) were followed in the selection of patients; namely, evidence of progression of the disease and one clinically healthy macula.[1]

Ophthalmological examination may show so much retinal and macular damage, the patient is informed pituitary surgery will probably not help, and no further testing is necessary. If eye involvement is not significantly advanced, the patient is scheduled for reevaluation in 2 to 3 months. If examination indicates deterioration of vision and progression of retinopathy, the patient is referred for systemic and endocrine evaluation.

These patients are further examined in the Neuroendocrine Clinic at UCLA School of Medicine by a team of physicians including neurologists, endocrinologists, psychiatrists, neurosurgeons, and gynecolo-

[1] See Table IV, p. 352.

gists. Following each clinic session, all patients are discussed in a formal group meeting. Each physician representing a different medical specialty expresses his opinion as to suitability of the patient for cryohypophysectomy.

Psychiatric workup

Patients are also referred to the psychiatrist who decides upon the patient's motivation and capability to insure flexible but effective control of his diabetes mellitus. This becomes particularly important in the postcryohypophysectomy phase, when insulin requirements fall and hypoglycemia may be one of the main complications. The psychiatrist spends sufficient time with the patients to assess their personality structures with particular reference to irrational behavior and suicidal tendencies.

Neurological workup

All patients are seen by a neurologist who assesses the extent and progression of the neuropathy, if any, and makes a careful survey of central nervous system functions including skull films and electroencephalography.

Endocrine evaluation

Preoperative and periodic postoperative endocrine evaluation includes PBI, T_3 uptake, cholesterol, radioactive iodine uptake, urinary gonadotropins, vaginal smear for estrogen effect in females, urinary 17-hydroxysteroids and 17-ketogenic steroids, water deprivation test, and recently radioimmunoassay of growth hormone with oral glucose tolerance and intravenous insulin-glucose tolerance tests. Occasionally the metapyrone test is performed during post-procedure evaluation.

Neurosurgical procedure

The freezing instrument is a vacuum-type, 2.7-millimeter diameter Linde cryoprobe and a liquid nitrogen system. The pituitary gland is particularly adaptable to freezing without damage to adjacent structures because of its generous blood supply, especially in the pars intermedius and surrounding cavernous sinus and carotid artery systems. Although the cryoprobe tip is usually reduced to −180° C., the measured tissue temperature at 7 millimeters from the probe tip is only −12° C. to −15° C.

Preparation for surgery

For 2 or 3 days prior to surgery the patient is prepared by using hexachlorophene (Phisohex) shampoos and frequent cleansing with 0.25 percent Neosynephrine nose drops and bacitracin solution (500 U per cc.). To prevent injury to structures adjacent to the pituitary gland, the patient is kept semiconscious during the making of the pituitary lesions. Much time is spent preoperatively therefore, in describing the procedure and in teaching hand signals for use during surgery. The operation is performed under "amnestic analgesia" using topical anesthetics with an endotracheal tube in place and supplementary intravenous meperidine and hydroxzine pamoate, as needed for patient comfort. The patient's head is aligned in a stereotaxic headholding unit. The sagittal plane of the head is perpendicular to the base of the instrument, and the transverse plane of the skull is in the axis of the arc system.

Lateral and anteroposterior X-ray films are taken to determine the exact measurements required for proper placement of the drill holes and cryoprobes into the sella turcica. The configuration of the pituitary gland and the position of the carotid arteries are determined by previous cavernous sinus venograms or carotid angiograms (*17*). When alignment is exact, twist-drill holes are made transnasally through the sphenoid sinus in the floor of the sella 4 to 5 millimeters to the right and left of the midline to allow passage of the cryoprobes into the anterior half of the pituitary. Prior to making the twist-drill holes, the nasal cavity and sphenoid sinus are again prepared with Neosynephrine and bacitracin solutions. The cryoprobe, in its guide and holding system, is then inserted into the desired region of the pituitary, and freezing is commenced. Figure 1 shows an X-ray of the cryoprobe in position in the anterior hypophysis.

Operative procedure

The temperature in the silver-tipped cryoprobe is reduced to 0° C. to determine if any adverse effect occurs. It is then taken slowly to the level of —180° C. This level is maintained for 5 to 10 minutes for each lesion, with generally two lesions made on each side in the anterior and posterior portions of the anterior pituitary (fig. 2). The system is then shut off with rewarming.

Surgical complications

Surgical complications in 31 diabetic patients have been minimal. There have been no permanent ocular or extraocular palsies. During

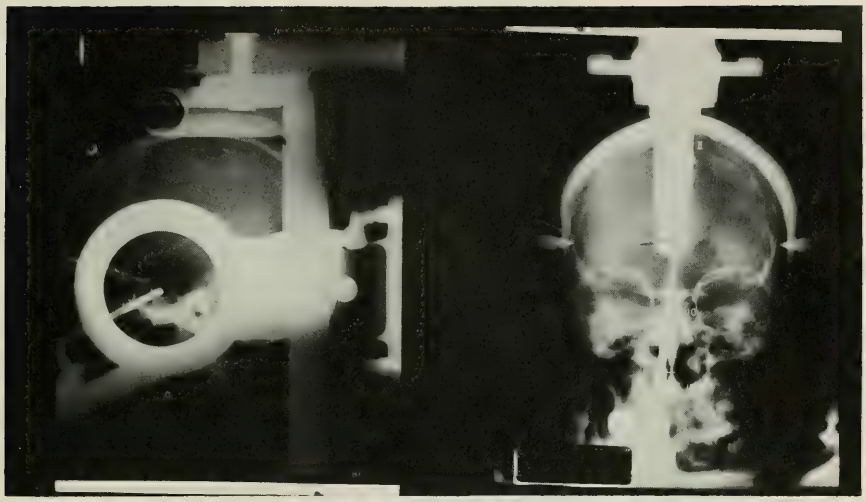

FIGURE 1.—*Lateral and anteroposterior roentgenograms of cryoprobe in the anterior hypophysis of patient during cryohpophysectomy.*

the operative procedure on patient 18, the drill on the stereotaxic device broke and had to be removed. The operation was discontinued and hypophysectomy was not completed. A second surgical procedure was later performed on this patient and a complete hypophysectomy obtained. During the operative procedure on patient 25 a nasal turbinate was damaged resulting in severe epistaxis and rhinorrhea. The patient was readmitted to the hospital and adequate packing of the area performed. No meningitis resulted. Patient 17 developed an inappropriate antidiuretic hormone syndrome with water intoxication and was readmitted to the hospital for appropriate treatment. This same patient is listed as having an incomplete hypophysectomy and has gone on to additional vitreous bleeding and visual loss. Patient 19 developed hypoglycemia while on DBI. Chronic diabetes insipidus developed in two patients, 7 and 20. Transient (1 or 2 days) postoperative diabetes insipidus occurred in approximately 25 percent of the patients, but was no problem and often antidiuretic hormone was not needed. Nasal packing is now performed routinely after the operative procedure. There has been no operative mortality.

Patients (see Appendix G)

Thirty-one patients with diabetic retinopathy have been operated by stereotaxic cryohypophysectomy. There are 18 men and 13 women, ranging in age from 23 to 58 years, with an average of 38.0 years at the time of surgery. The postoperative followup ranges from 1 to 49 months. The average age at the time of diagnosis of diabetes mellitus

FIGURE 2.—*Photograph of patient in stereotaxic headholding apparatus undergoing cryohypophysectomy. Note the state of wakefulness which allows study of ocular functions during the production of cryogenic lesions to avoid palsies.*

was 18.8 years and the average at the time of first eye symptoms was 36.7 years. Four patients died;—patient 1 of renal failure 25 months following surgery. His ocular function was stable at the time. Patient 8 died 4½ months after surgery of a myocardial infarction and previously undiagnosed severe coronary artery disease. He had exhibited improvement in diabetic retinopathy and in visual acuity of the left eye. Patient 11 died 30 months following surgery of a myocardial infarction. This patient had shown some improvement in vision until she received trauma to the left eye followed by a secondary retinal detachment. The vision in the right eye had improved at first and then had deteriorated. Patient 5 died 38 months following surgery. We have been unable to determine the cause of death. Vision had improved in this patient.

RESULTS

Endocrine responses and management (Table I)

Adequate postoperative endocrine studies are available for 25 patients. Endocrine and clinical evidence of complete hypophysectomy is apparent in 21 of the 25 patients with two "borderline complete" and two apparently "incomplete." This evaluation is based on the finding of hypothyroidism (low RAI uptake and/or PBI) plus low urinary gonadotropins for "complete" hypophysectomy and only one of these below normal for "borderline complete" hypophysectomy. Adrenal function was not retested in most of the patients postoperatively.

In general, the endocrine management has been no problem (Table I). All patients are started on intravenous hydrocortisone hemisuccinate at 10 milligrams per hour just prior to hypophysectomy and continued parenterally for 1 to 2 days postoperatively. Within 4 to 7 days the dose is rapidly reduced to maintenance Prednisone by mouth at 5 to 10 milligrams per day. Hypoadrenal crises have been very infrequent. All of the patients have remained on maintenance Prednisone. Desiccated thyroid is given after 3 to 4 weeks, but only if thyroid function tests and clinical signs and symptoms indicate hypothyroidism. Twenty of the 26 patients required desiccated thyroid with satisfactory euthyroidism. Patient 8 was hypothyroid but died of a myocardial infarction before thyroid was given. The other five patients were not clinically hypothyroid. Gonadal hormone replacement has been given for clinical deficiency symptoms. Five of the 10 women with adequate followup received estrogens and six of 16 men testosterone. One patient requires vasopressin nasal spray regularly for chronic diabetes insipidus. The diabetes mellitus is carefully evaluated and controlled before and following hypophysectomy. As is common, most patients have had a significant reduction in their posthypophysectomy insulin requirements. Insulin requirements were reduced in

TABLE I.—*Posthypophysectomy endocrine replacement and diabetic therapy*

Drug	Possible patients	Patients treated taking
Adrenal steroids	26	26
Thyroid	26	20
Estrogens (F)	10	5
Testosterone (M)	16	6
Pitressin	16	1
Insulin	26	
Reduced		25
Same		1
Chlorpropamide	2	
Reduced		2

25 of 26 patients evaluated with one unchanged. The average change of insulin requirement was 20 units, with a range of 8 to 40 units. There was no change in two patients on insulin. In the two instances in which patients were on oral therapy, it was possible to reduce the dose to one-fourth the preoperative level with better control. One patient, 16, who was followed elsewhere, developed cholestatic jaundice 6 months after surgery secondary to oral methyltestosterone. After discontinuing this drug, the jaundice subsided.

Ocular responses

The changes in visual acuity for each patient are listed in Appendix G. Based upon these facts and upon the retinal appearances, the ocular responses in the time of followup in the 26 patients are: improved or unchanged, 21; progression, five.

Therefore, including patients with improved and stable retinopathy, 81 percent had a successful ocular response following cryohypophysectomy, considering that all patients exhibited progressive retinopathy before surgery. Dramatic visual and funduscopic improvement was observed in three of the improved group (patients 6, 14, and 15) most of whom showed a rapid response after surgery.

Adequate postoperative information is not available on patients 23, 27, 28, and 29 to estimate ocular status. Patient 24 had poor vision before surgery, due to marked vitreous hemorrhage. Although the visual acuity is unchanged postoperatively, we cannot be sure of the effect of the hypophysectomy since obscuring hemorrhage and fibroproliferation still persists. Patients 1, 20, and 22 had progression of disease in one eye, while the remaining eye showed improvement. Of 52 eyes evaluated, 40 showed improvement or were unchanged, and 12 eyes showed progression of disease.

Since the O'Hare Classification [1] is new to us, an attempt to classify the fundi of our patients, preoperative and postoperative, is somewhat uncertain. We have attempted to do so, however, and we show the following results: we were able to classify the same 38 eyes, before and after surgery. All preoperative patients showed some element of proliferative retinopathy. One postoperative patient showed no proliferative retinopathy after clearing of marked vitreous hemorrhage in each eye. Table II shows the incidence of each element of the classification in the 38 eyes involved. In the postoperative classification a higher percentage of the N_1 classification appears compared to the preoperative evaluation. This also holds true for the absence of vitreous

[1] O'Hare Classification, p. XXI.

TABLE II.—*Incidence of components of O'Hare Classification (38 eyes)*

PREOPERATIVE 38 EYES

	B	N_1	N_2	F_0	F_1	F_2	H_0	H_1	H_2
Number of eyes		15	20	6	14	14	5	28	5
Percentage of total		38.4	52.6	15.8	36.8	36.8	13.5	73.6	13.5

POSTOPERATIVE 38 EYES

	B	N_1	N_2	F_0	F_1	F_2	H_0	H_1	H_2
Number of eyes	2	20	12	6	13	12	26	7	5
Percentage of total	5.3	52.6	31.6	15.8	34.2	31.6	68.4	18.4	13.5

hemorrhage in the postoperative as compared to the preoperative classification.

Table III shows the average length of time for retention of vision following surgery in 52 eyes to be 14.71 months. Comparing this with an average of 19.08 months followup, we find a visual retention index of 0.77.[1]

No correlation of response can be made with the degree of satisfactory hypophysectomy in our current series. The one patient who endocrinologically and clinically had an incomplete hypophysectomy (No. 9) had improvement of his retinopathy. In the two patients with a borderline complete hypophysectomy (Nos. 3 and 12), one progressed and the other improved. One patient (No. 13) who progressed had no measurable growth hormone detected three months after surgery following an insulin-glucose tolerance test. Her other postoperative endocrine tests also indicated complete hypophysectomy. It should be noted that in two of the five patients whose retinopathy progressed (Nos. 11 and 13), there was initial rapid improvement, but 18 and 4 months, respectively, following hypophysectomy their retinopathy deteriorated rather abruptly. Both of these patients had evidence of complete hypophysectomy. In all cases an effort is made to produce total adenohypophysectomy preserving the posterior lobe complex.

Figure 3 shows the preoperative fundus photograph of a 32-year-old man (No. 15) who had diabetes for 18 years with failing vision for 6 to 8 months. It shows extensive hemorrhages, exudates and microaneurysms. The same area of the left retina is demonstrated 3 months after cryohypophysectomy in figure 4. Considerable clearing of the retinopathy is observed, and visual acuity is markedly improved.

TABLE III.—*Visual retention index (52 eyes)* [1]

	Average
Months vision retained after surgery	14.71
Months followup	19.08
V. R. index	0.77

[1] Visual retention index, p. 265.

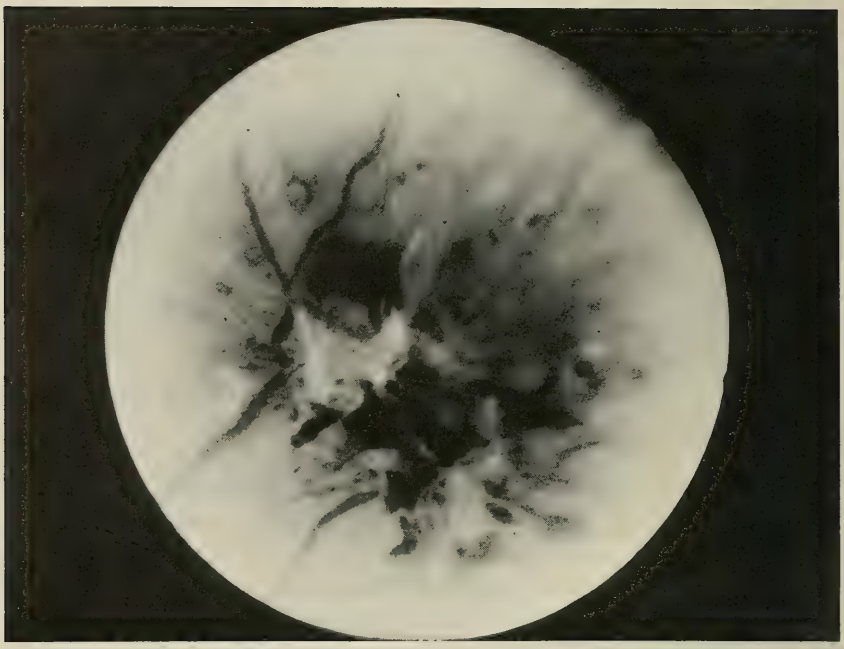

FIGURE 3.—*Preoperative fundus photograph of 32-year-old male diabetic showing extensive hemorrhages, exudates, and microaneurysms.*

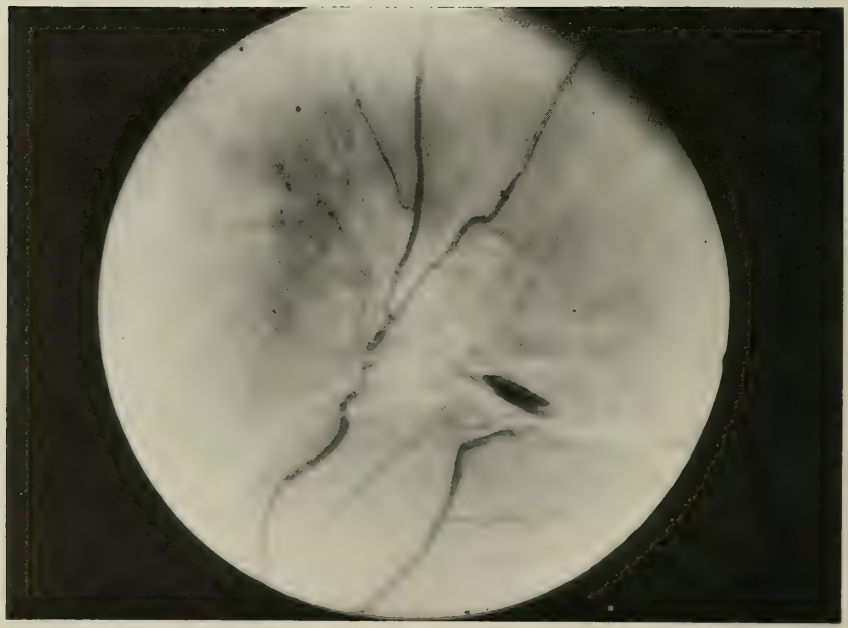

FIGURE 4.—*Fundus photograph of same area of retina 3 months after cryohypophysectomy, demonstrating considerable improvement in his retinopathy.*

DISCUSSION

Our experience indicates that stereotaxic cryogenic hypophysectomy is an effective, simple, and safe technique of pituitary ablation in diabetics with progressive retinopathy. There has been no operative mortality and no serious morbidity. These figures are considerably more favorable than the 11 percent operative mortality reported in 1962 in a collected group of 134 patients who mainly had neurosurgical procedures (*18*). Recent surgical experience, however, has been considerably improved (*5*, *7*).

Our present results showing 81 percent of the patients with satisfactory ocular response compares favorably with other reported series (*5*, *9*, *11*, *12*, *19*, *20*).

It is apparent at this time that the several methods of hypophysectomy can benefit a reasonable number of patients with progressive diabetic retinopathy. The question of how this radical treatment accomplishes a slowing of the progress of diabetic retinal angiopathy remains unanswered. Improvement in blood glucose control, since insulin requirements are generally lowered, lowering of growth hormone levels, and changes in cortisone secretion have all been considered as playing a role. How these or other metabolic alterations inhibit the progression of diabetic retinopathy, if at all, awaits further investigation.

Another question is whether total hypophysectomy is necessary to improve retinopathy. Most workers feel complete pituitary ablation is essential, since many patients with only a partial destruction are not improved. However, Joplin and associates (*11*) indicate that complete hypophysectomy is not necessary in all cases, and in our experience some patients did not have evidence of total hypophysectomy, but their retinopathy appeared to improve. Nevertheless, at this time we do attempt to accomplish complete anterior pituitary destruction while awaiting further evaluation.

What effect hypophysectomy might have on the angiopathy in other organs, such as the kidney, heart, and peripheral vessels, likewise needs further determination. Pearson and associates (*4*) suggest the nephropathy might be helped by hypophysectomy since the blood urea nitrogen fell from mildly elevated to normal levels in two of three patients after surgery, and there was no renal deterioration up to 6 years followup in their patients. However, Lundbaek and coworkers (*19*) noted no beneficial effect in any other manifestation of long-term diabetic vascular disease in their controlled series other than the improved ocular responses. One of our patients whose retinopathy improved died of renal failure 2 years after surgery. Kidney function has re-

mained stable in the majority of our other patients during the period of followup, but progressive azotemia has been noted in a few. The appearance of renal tissue by light and by electron microscopy in six diabetics, before and 1 to 2 years after pituitary ablation for diabetic retinopathy, has recently been reported by Ireland and associates (*20*). They noted a significant reduction in the thickness of the glomerular capillary basement membrane, improvement in endothelial and mesangial cells, and no improvement in the arteriolar lesion. Further studies of serial renal biopsies before and after hypophysectomy are needed to clarify these problems.

TABLE IV.—*Ocular standards for patient selection for cryohypophysectomy*

1. Evidence of progressive retinopathy.
2. At least one clinically healthy macula.
3. Corrected visual acuity should be no worse than 20/60 to 20/80 in the better seeing eye.

Patient 24 was selected for hypophysectomy even though the macular areas could not be accurately evaluated due to marked vitreous hemorrhage. However, acuity immediately prior to the vitreous hemorrhages suggested the macular areas should be clinically healthy. Nevertheless, the patient has not done as well postoperatively as expected. This again points up the necessity for careful and proper evaluation of the macular areas. Patient 12, who was considered a borderline candidate from an ophthalmological viewpoint, showed no improvement in vision. Several weeks delay occurred in securing hospitalization and in scheduling surgery, during which time hemorrhage in the vitreous increased. Patient 13 has also done poorly. Vitreous and retinal hemorrhages were noted to recur after the patient had experienced improved vision for 4 months following surgery. Of possible significance is the postoperative occurence of numerous insulin reactions. Patient 17 has also done poorly. This patient had light coagulation in the left eye prior to cryohypophysectomy. As retinal hemorrhages increased, cryohypophysectomy was advised because of progressive disease in the patient's only usable eye. Postoperatively he developed an inappropriate antidiuretic hormone secretion syndrome. During this time he experienced severe vitreous hemorrhages which took months to clear and resulted in more fibroproliferation and subsequent visual loss.

There is still a predominance of men in our series, 18 to 13. The average patient age of 38 years at the time of surgery indicates again that we are dealing with the juvenile diabetic. Four deaths in our series are due mainly to myocardial disease. The degree of visual and funduscopic response varies as illustrated by the dramatic improvement in patients 6, 14, and 15. Patients 1, 20, and 22 had progression

of disease in one eye with the remaining eye showing improvement. The O'Hare Classification shows we are suggesting surgery only for patients with proliferative retinopathy. Using the same classification, we see in our series that there is a reduction in new vessel formation and vitreous bleeding. Although the classification of fibroproliferation may be unchanged after surgery, there is still an impression of a thinning or an attenuation of the fibroproliferation. The fibroproliferation may change from a very dense white state to a thin, filmy one. Patients with advanced medical problems, such as severe cardiac disease or advanced nephropathy, are not good candidates for this procedure.

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CHAPTER 30

Pituitary Stalk Section for Angiopathic Diabetic Retinopathy: Technique, Mortality, Morbidty, Postoperative Management

WILLIAM H. SWEET, M.D., D. Sc.
RICHARD A. FIELD, M.D.

This is a discussion of lessons learned and of the results relative to the items in the title in the course of treating 121 diabetics by this operation between May 10, 1959 and September 19, 1966 inclusive.

TECHNIQUE

The features of the procedure as we have carried it out are as follows: A spinal puncture needle or catheter is placed in the lumbar intrathecal space. The patient is placed supine with both head and foot of the operating table elevated. A unilateral frontal exposure is made on the side of the eye with the worse vision. One of us (W. H. S.) finds that he can operate with equal dexterity (or clumsiness) from either side. Since in the presence of a prefixed chiasm, one may need gently to elevate the optic nerve on the side of the exposure and retract it laterally at its junction with the chiasm, it is preferable to do this on the side of the worse eye. The skin incision begins just behind the position of the normal frontal hairline 2 centimeters to the other side of the midline, following down along the line nearly to the zygoma on the side of the exposure. This permits forward reflection of the scalp nearly to the ipsilateral supraorbital margin without incising fibers of the frontalis muscle. The pericranium is incised transversely 2 centimeters above the proposed site of the low supraorbital saw cut. If frontal sinus is entered, the living anterior pericranial flap is sewn to the dura at the inferior frontal bone edge after a small, circa 5 by 5 centimeters quadrilateral flap of bone has been reflected laterally attached to temporal muscle. A linear incision in the dura above the supraorbital saw cut gives ample access as the frontal lobe falls back consequent upon hyperventilatory decrease in cerebral volume. Withdrawal of spinal fluid from below is deferred until the dura is almost exposed so that one can judge the amount of fluid one needs to remove.

In many of the first cases, an early withdrawal of 60 to 70 cubic centimeters of cerebrospinal fluid from below permitted an unnecessarily generous falling away of frontal lobes from the cribriform areas on both sides with elevation of both olfactory bulbs from the cranial base. We soon began to make a particular effort to conserve the contralateral olfactory pathways and often keep those on the ipsilateral side intact as well, by approaching the chiasm from anterolaterally. If the chiasm is normally or post-fixed and the stalk readily seen, the manipulations are carried out as the orbital surface of the frontal lobe is steadied with a hand-held flat retractor. A concealed position of the stalk leads to the placement of the Dott self-retaining type of retractor.

Having learned from a neurosurgeon elsewhere that one of his patients of this type developed a cardiac arrest during operation, recognized too late for effective resuscitation, we have visual and auditory monitoring of the heartbeat throughout the procedure. The gentle sound of the regular heartbeat is soothing rather than disturbing to the surgeon, whereas a burst of irregularity alerts the whole team and we wait for the cardiac rhythm and electrocardiogram to resume their earlier state before resuming our manipulations.

From the first case on we have sought to preclude or delay regeneration of neural and vascular components of the stalk by singly or doubly clipping this structure and by interposing a gold plate 0.33 millimeter thick and of appropriate length and width, usually about 10 by 10 millimeters square, between the hypothalamic end of the stalk and the diaphragma sellae. It lies underneath the optic nerves and chiasm (fig. 1a). In the early part of the series we drew the stalk gently downward and forward seeking to place the higher clip and the cut as near the hypothalamus as feasible, 6 to 10 millimeters above the diaphragma. When we can see the tuber cinereum, we place the clip just beneath it. However, we realized that the hypothalamic end of the cut stalk tends to fall forward toward the sella. One patient who had not lost her menstrual or thyroid functions after stalk section had a recurrence of her retinal hemorrhages 11 months after their postoperative cessation. Our radiograph then showed that the clip on the hypothalamic end of the stalk lay within the sella inferior to the gold plate, having crept down behind it and just in front of the dorsum sellae (fig. 1b). This led us to make two changes in technique: (1) placement of the gold plate to overlap the top of the dorsum sellae, and (2) continued high clipping of the stalk, but cutting well below the clip so that we would have an ample length of stalk to lie on top of the gold plate and to be surrounded by gold foil (fig. 1c). A foil 0.0015 millimeter thick proves to be easy to handle and is vigorously adherent to the stalk and metal clip on it. Even when the stalk is cut

FIGURE 1a.—*Gold plate above diaphragma sellae overlapping top of dorsum sellae. Clip above plate on hypothalamic end of stalk; clip below plate on stalk at diaphragma sellae illustrating depth in sella at which diaphragma may lie. Patient Lawrence B.*

FIGURE 1b.—*A single clip on hypothalamic end of stalk shows that this lies below the gold plate. At reoperation the stalk was found firmly reattached to pituitary gland. Patient Gloria G.*

FIGURE 1c.—*Current technique of placing clip high on hypothalamic end of stalk, cutting stalk at diaphragm and wrapping it with gold foil distal to clip and above gold plate. Patient William B.*

beneath the optic chiasm, and the hypothalamic end eases back out of direct view, the appropriate position of the clipped stalk can be checked by seeing its reflection in the shiny gold plate beneath it. In order to prevent the plate from falling backward into the prepontine cistern it is tethered by a single silk stitch to the dura of the planum sphenoidale, its anterior edge being held against the tuberculum sellae. A fast drying, nontoxic liquid plastic such as Aron S. Alpha may prove superior if it does not break down after years of exposure to cerebrospinal fluid.

In no patient has it been necessary to consider cutting an optic nerve to facilitate identifying the stalk. However, we have not infrequently been unable to see it until we gently felt for it beneath the chiasm with a right angle delicate, dull nerve hook and brought it forward into view by simultaneous slight retraction of the ipsilateral optic nerve with the shaft of the hook. As a consequence of the parallax related to the oblique view of the chiasmal region, the stalk lies more nearly in the line of sight of the inner angle of the junction of nerve and chiasm than in that of the middle of the chiasm. On a few occasions in which a high-lying diaphragma lay close to a prefixed chiasm, we removed a little of the antero-superior part of the gland in order to find the stalk and have room to slip in the gold plate.

Once, in the presence of a markedly prefixed chiasm, it proved simple to see and cut the stalk from a lateral view above the supraclinoid internal carotid and below the gently elevated optic nerve and chiasm. An arterial strand, tiny even under 2x magnification, passing up from the artery to the optic tract was lightly coagulated and divided. Postoperatively this patient had a new, complete and persistent temporal hemianopia in his opposite good eye innervated by the optic tract in question. Thereafter every effort was made to save every identifiable vessel to the visual pathways, no matter how minute, in this and all other types of surgery in this region. In most of the operations for stalk section not a single bleeding point has developed during the intradural phase of the procedure. On one of the only two other occasions in which we have elevated the lateral aspect of the chiasm and cut the stalk from the lateral approach above the carotid artery, we produced a large but not complete defect in both temporal quadrants of the contralateral eye which was nearly 10 months in clearing. This occurred despite no identified injury to any tiny vessel, but we did demonstrate the view to a series of observers. A brief, minimal elevation of the chiasm seems advisable if this approach is used.

Closure in the first part of the series included placement of the bone dust in the medial burr holes and interrupted silk to the temporal fascia and galea. However the development of wound infections (*Staph. aureus*) in three of the first 28 cases has led to the use of fine catgut in place of silk for the buried extracranial stitches; to suture of living pericranium over the antero-medial burr hole without bone dust, and to injection of 10,000 to 15,000 units of bacitracin in 10 to 15 cubic centimeters of fluid beneath the scalp flap after the fine wire closure of the skin was completed. There have been two minor wound infections confined to the scalp in the last 92 cases.

EARLY MORTALITY

There were three deaths during the first 3 postoperative months, all with post mortem examinations. None were directly related to problems in the head or brain. One 40-year-old lady, alert, active, and eating well on her first postoperative day, had an abrupt cardiovascular collapse on her second morning, dying in 30 minutes in a myocardial ischemic episode. Another 28-year-old lady awoke from her anesthesia with a low anterior spinal artery syndrome characterized by paraplegia and analgesia up to midtorso with preservation of touch and proprioception. Although these signs were clearing, she died abruptly of a massive pulmonary embolus on her 34th postopera-

tive day. The third relatively early death occurred in a 41-year-old man who left the hospital on his 17th postoperative day following an uneventful early convalescence. He had returned to his work and active life only to die of a pulmonary embolus on his 79th postoperative day, having had a few unrecognized warning symptoms in the previous week.

POSTOPERATIVE MORBIDITY

General stress of the procedure: An indication of this, plus the time required to teach the patient how to care for himself, can be gleaned from the average hospital stay of 18 days postoperatively. This figure includes the seven patients whose postoperative period was from 30 to 40 days.

Wound infections: There were infections of the craniotomy site, all with *Staphylococcus aureus*, two early and one late, in the first 28 cases. The latter required removal of the bone flap to control it; a brief period of open drainage and antibiotics sufficed in the first two. Improvements in technique reduced the incidence in the last 92 patients to two minor scalp infections handled promptly only by antibiotics.

Urinary tract infections: There were 24 of these, partially related to use of an inlying catheter during the major diuresis of the first few postoperative days. No major complications followed any of these urinary infections, all treated by the antibiotics dictated by the sensitivities of the cultured organisms.

Miscellaneous toxi-infectious states: In this category there were three patients with upper respiratory infections and one with hepatitis and parotitis. There were two aseptic meningeal reactions related to placing about 10,000 units of bacitracin crystals external to the closed dura—a tactic which was promptly discontinued.

Worsening of vision caused by operations: The fact that we operated on the side of an eye which was legally blind in 74 percent of the cases diminished the frequency of ascertainable operative trauma to the visual pathways. In only one of the 117 patients (Donald H.), in whom we approached the stalk between the optic nerves, was there a new postoperative field loss. This was a partial temporal defect in the eye ipsilateral to the bone flap, which defect, along with decreased visual acuity, had cleared by the 12th postoperative day. Our two longer lasting, temporal hemianopias in the opposite better eye following a lateral approach to the stalk were described under techniques.

Cerebral ictus: There were episodes whose nature and course led to the diagnosis of cerebral ischemia in five patients. The three more

serious ones occurred in men aged 38, 29, and 38 years on the fourth, 10th, and ninth postoperative days and cleared within 24, 3, and 6 days respectively. In each there was the abrupt onset of a motor and sensory aphasia and in the longest-lasting instance there was also a right lower facial weakness and agraphia. Absence of weakness in an extremity and prompt early lessening of the signs made it unnecessary to reopen the wound in any of them. The first patient with the worst ictus (George M.) was one of the poorest candidates for operation in the series on the basis of his renal and cardiovascular studies, and on the day of his cerebral ictus also began to develop EKG changes indicative of subendocardial injury. In the second patient (Robert Mc.) we had on his ninth postoperative day permitted his fluid intake to fall 1,600 cubic centimeters behind his urine output of 3,900 cubic centimeters. His aphasia cleared rapidly as his fluid and electrolyte balance was restored. In the third patient (Charles W.), we inadvertently omitted on his eighth postoperative day the last two of his three doses of 100 milligrams of Dilantin, which we routinely give to patients with supratentorial craniotomies. Early on his ninth day he had a generalized seizure with a 6-day postictal aphasia. The other two episodes were minor and cleared rapidly.

Postoperative edema or hematoma: Major concern about these two possibilities did not come up in any patient, and hence no wound was reopened for purposes of decompression or evacuation of clot.

Convulsions: Two patients early in the series had a convulsive seizure following operation; we successfully precluded any such episode in the remainder of the series by using Dilantin 100 milligrams t.i.d. for some weeks after the procedure.

Anosmia: We deprived six patients of their olfactory function bilaterally before we realized that too generous a use of hyperventilation and withdrawal of cerebrospinal fluid could let the opposite frontal lobe lift its olfactory bulb up out of the cribiform area as it fell back. A contralateral loss of olfaction was avoided in all but two patients thereafter. Without embarrassing our pursuit of the operation's main objective, we have recorded saving the sense of smell even on the ipsilateral side in 29 patients in the series.

Fever: Of 100 patients whose temperature charts were checked, 93 had elevations of rectal temperature to 100° F. or more on at least one reading postoperatively. There was an average of 4.4 days per patient on which such elevation occurred. In no patient was hyperpyrexia a significant problem.

Postural hypotension: This problem, sometimes seen after total hypophysectomy, was not responsible for clinical symptoms in any of our patients.

MANAGEMENT IN HOSPITAL

In this series nearly all of the patients had renal biopsies usually secured at open operation. The open procedure, as contrasted with needle aspiration, not only yielded a better specimen but as well was free of the complications of hemorrhage (Leadbetter, J.A.M.A. 1966 [1]). The other features of our endocrine, cardiovascular, renal, ophthalmological, neurological, psychological, and general medical appraisal have been described much earlier along with the criteria therefrom for the selection of patients. Any of the following findings (Field et al., Diabetes, 1962) led to rejection of the patient for operation: [2]

(*a*) Creatinine clearances consistently below 60 L per 24 hours; [2] fixed azotemia; serum albumin below 2.5 grams percent; a predominant element of pyelonephritis in renal biopsy; more than moderately advanced arteriolar disease or hyalinization of glomeruli; and refractory urinary tract infection.

(*b*) Fixed cardiomegaly, extensive or active myocardial infarction, overt or borderline cardiac failure, fixed arrhythmia, or angina pectoris.

(*c*) Chronic, ineradicable infection anywhere.

(*d*) Incapacitating peripheral or visceral neuropathy.

(*e*) Personality, character, or emotional instability, or intellectual deficit of a degree that indicated inability to adhere to a demanding regimen of medication, diet and periodic examination. An important, almost intangible criterion is the intensity of the patient's motivation toward the procedure. Unless there was clear understanding of what was involved and a positive, affirmative choice without persuasion was evinced, the patient was not offered the procedure although all other criteria were fulfilled.

Our ophthalmologic criteria are described in chapter 26 of this book ("Hypophyseal Stalk Section as Treatment for Diabetic Retinopathy. Ocular Aspects").

Hydrocortisone was given as follows: 25 to 50 milligram dose by mouth the evening before operation, 50 to 75 milligrams intramuscularly shortly before operation, and 25 milligrams instramuscularly every 8 hours for the first several days postoperatively. This was reduced stepwise to a dose at discharge of 10 milligrams orally three times a day.

Vigilant attention to the fluid, electrolyte, and carbohydrate metabolism included a personal visit by the physician at least three times a day. To avoid mistakes in measuring fluid balance, inlying Foley catheters were used to collect urine. An hourly, cumulative in-

[1] Reference 1.
[2] Reference 2.

take and output chart of fluids was kept, the objective being to increase intake to match any abrupt diuresis and avoid hypovolemia. A tenfold increase in urinary excretion in 2 successive hours was not uncommon. We sought to avoid a vasopressin provoked water retention, hyponatremia and cerebral edema, using this hormone only if urinary output exceeded 300 cubic centimeters per hour over 2 successive hours. At first Na, K, Cl, hematocrit and serum osmolarity were checked daily. We sought to err on the side of slight dehydration as indicated by the fact that a level of serum Na greater than 145 milliequivalents per l was recorded at least once in 47 of our patients. However the Na level did slip below 130 milliequivalents per 1 on 1 or more days in 27 of the patients, usually after we had stopped daily determinations in the second and third postoperative week. The 24 hour urine volume was allowed to exceed 3000 cubic centimeters one or more times in 13 patients. During the hospital stay in 79 percent of the patients, one or more doses of Pitressin were given; in only 21 percent were more than five doses required. Nor did the management of the diabetes insipidus ever present a significant problem after discharge from the hospital.

In a few patients a temporary salt-losing syndrome was demonstrated by the serum and 24 hour urine determinations and NaCl tables, 1 gram several times a day, were given. Abrupt appearance of drowsiness or stupor may be on either a hypernatremic or hyponatremic basis, and we have seen both states successively in the same patient. No chronic problem on these scores developed, despite the not infrequent application of the high clip just below the visualized tuber cinereum.

SUMMARY AND CONCLUSIONS

Our methods for carrying out section of the pituitary stalk and for managing patients before, during and after the operation are described on the basis of 121 such operations. The early mortality of three patients in the first 3 postoperative months was not caused by any cephalic or cerebral problem. The numerous causes of morbidity are described in detail; assiduous medical surveillance prevented these from leading to catastrophe.

It is our impression that transfrontal stalk section presents significantly less stress to the seriously ill diabetic than does total hypophysectomy via the transfrontal route. We present in chapter 20 (Field, McMeel, Sweet, and Schepens) the basis for our tentative conclusion that the long-term preservation of vision is at least as satisfactory after stalk section as after hypophysectomy.

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CHAPTER 31

Radiofrequency Pituitary Ablation (Its Use in Diabetic Retinopathy)

NICHOLAS T. ZERVAS, M.D.
PHILIP D. GORDY, M.D.
RICHARD A. FIELD, M.D.

In 1954 Talairach first described the transsphenoidal stereotaxic approach to the hypophysis (*1*, *2*). Because Talairach's method involved minimal stress and operative risk, others eagerly adopted it (*3*, *4*, *5*). In earlier cases radioactive isotopes, primarily Yttrium-90, were used as destructive agents; experience revealed, however, that cerebrospinal fluid rhinorrhea complicated installation of these isotopes in 3 to 37 percent of cases (*3*, *4*, *5*, *6*). Jadresic (*6*) noted that cerebrospinal fluid rhinorrhea followed transcranial administration of Yttrium-90 through a frontal burr hole. His observations indicated that necrosis of the floor of the sella was a major factor in the production of rhinorrhea, and that this occurred whether or not there was a surgical lesion of the floor.

Radiofrequency hypophysectomy takes advantage of Talairach's innovations but avoids at the same time the complications of internal radiation (*7*, *8*). The RF electrode design permits overlapping radial lesions through a single midline 2 millimeter puncture in the anterior wall of the sella turcica. During the past 5 years 141 cases of radiofrequency thermal hypophysectomy have been carried out. With experience and modifications the procedure has become safe, simple, effective, and easily tolerated by even seriously ill patients.

ANATOMICAL STUDIES

In order to bring about maximal ablation of the pituitary, a stereotaxically oriented anatomical study of the sella turcica was carried out. Although statistical series of the size and shape of the hypophysis and sella turcica have been reported in the past, none has taken into account factors important to the stereotaxic method (*9*, *10*). To do this, the relation of the hypophysis to the sella turcica in 97 cadaver specimens was studied as a function of the radiologic appearance, the gross morphology, and the histologic anatomy of the cadaver specimens.

At the time of autopsy, the sphenoid bone was removed with care

taken not to damage the sella turcica. The following lengths were noted:

(1) Dorsum—tuberculum.
(2) Transverse hypophyseal diameter.
(3) Dorsum—posterior edge of pituitary stalk.
(4) Tuberculum—anterior edge of pituitary stalk.
(5) Intraoculomotor nerve distance, inter-carotid artery distance.
(6) Diaphragm—floor of sella.
(7) Interanterior clinoid distance.
(8) Hiatus of diaphragma sellae.

Radiographs were then taken in the fresh state in the sagittal and frontal planes. The radiographs were then repeated after the diaphragma sellae was coated with tantalum dust to outline that structure on radiographs (fig. 1). Coronal films were taken after dissection and marking of the lateral tips of the hypophysis with a radio-opaque indicator. Depending on the configuration of the radiographs, the specimens were then chosen for serial histologic sections in either the frontal plane or sagittal planes. Specimens were demineralized in five percent nitric acid, fixed, embedded, serial sectioned and stained appropriately.

To assess shrinkage or swelling during fixation, spaced dyemarkers were placed in the gland, 4 millimeters apart; this was done prior to fixation in order to indicate distortion. In a few specimens the pituitary was dissected free in the fresh state under the dissecting microscope and was weighed and measured carefully. Following fixation and passage through all histological preparatory states prior to paraffin embedding, it was reweighed and remeasured. The distortion in most cases was minimal when routine fixation with 10 percent buffered formalin was used. The pertinent measurements noted above were repeated when possible, and, in addition, the following were noted:

(1) Dorsum sella—anterior edge of neurohypophysis.
(2) Dorsum sella—insertion of pituitary stalk.
(3) Height of insertion of pituitary stalk above floor of sella.
(4) Position of anterior margin of diaphragma sellae in relation to anterior pole of the pituitary.
(5) Sagittal length of neurohypophysis.
(6) Sagittal length of adenohypophysis.

A full report of this study will be published shortly. Some preliminary, pertinent observations are noted below. These studies failed to demonstrate reliable radiographic indicators of the height or sagittal length of the hypophysis. The width of the pituitary was found to correspond well, however, to the width of the floor of the sella. On frontal radiographs, the floor turns down on either side where it joins the lateral wall of the sphenoid sinus. In most cases the angle

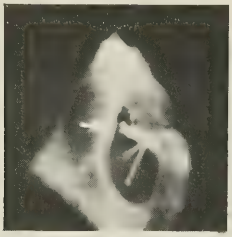

FIGURE 1.—*Note tantalum dust lining surface of diaphragma sellae. Arrow indicates tuberculum sellae. Markers indicate insertion of pituitary stalk. (Magnified x 1.15.)*

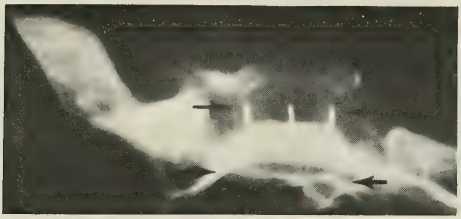

FIGURE 2.—*Anteroposterior radiograph. Lower arrows indicate lateral crests of sellar floor. Upper arrows point to upper edge of markers placed at lateral pole of pituitary. Angulation could not be avoided, but upper point of each marker was correctly in position. (Magnified x 1.15.)*

FIGURE 3.—*Coronal serial section. Note medial displacement of carotid artery under lateral pole of hypophysis (arrow). Also observe deep depression in central portion of gland associated with perforate diaphragma sellae and deep intrasellar subarachnoid space. Further observe lateral position of oculomotor nerves with interposition of carotid arteries (double arrow). (Hematoxylin-eosin; no magnification.)*

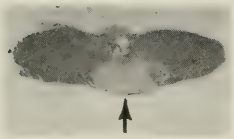

FIGURE 4.—*Horizontal section of hypophysis. Arrow points to pars nervosa. Note partial encirclement by adenohypophysis. (Hematoxylin - eosin; magnified x 2.)*

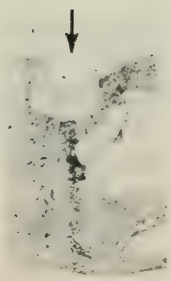

FIGURE 5.—*Serial section of decalcified sella in patient who died of meningitis. Arrow points to sella turcica. Higher power examination revealed sparsely cellular fainty pink staining connective tissue. (Hematoxylin-eosin; no magnification.)*

formed by the sphenoid wall, and the sellar floor was well visualized, and often marked by a slight peak or ridge. The lateral poles of the hypophysis in almost all cases were found to lie within 1 millimeter of their angles (fig. 2). In some specimens, however, the slope of the floor falls off less acutely, permitting ambiguity to arise. In such cases it was found that the first downward angulation of the floor represented the true edge of the sella, and that the asymmetric extension represented a groove that accommodated the cavernous sinus and the carotid artery. The importance of recognizing this common variation and of staying within the primary angle of the floor should be obvious. A second point was that on frontal sections the relation of the cavernous sinus and the carotid artery to the lateral poles of the hypophysis was variable. In most cas esthere structures abutted the lateral hypopsysis. but in some the carotid arteries were 3 millimeters lateral to the hypophysis. These observations cast doubt on the reliability of cavernous sinus venograms or carotid arteriograms to describe faithfully the lateral margins of the hypophysis (fig. 3).

The position of the diaphragma sellae above the floor of the sella had no constant relationship to the bony shape of the sella. In a few cases it was above a line drawn from the most anterior edge of the dorsum to the tuberculum sella. In many cases the diaphragma was perforate, as has been noted by other studies (*9*, *10*), and in some specimens the diaphragma sellae lay deep in the sella. No satisfactory clue to this variation was radiographically apparent; although palpation with a spring probe at the time of operation could detect it (See below).

The position of the pituitary stalk was found to vary with the sagittal length of the sella turcica. In foreshortened glands the stalk lay well posterior, falling over the anterior edge of the dorsum sella; in elongated glands it descended onto the midportion of the superior surface of the gland well in front of the dorsum. To spare the stalk and to avoid diabetes insipidus, no lesions were made in the vicinity of the superior dorsum sella in any patient; and in elongated glands, the posterior one-half of the superior medial surface was left intact (table 1).

The neurohypophysis appeared generally as a nodular protrusion behind the adenohypophysis (fig. 4). The latter encircled the neurohypophysis somewhat as a socket couples with a ball joint. Despite the variability, it was noted that in the midline, the pars distalis could approach to within 2 millimeters of the dorsum sella, while laterally at 2 to 3 millimeters from the midline, it would often reach the dorsum sella. To insure total destruction of the adenohypophysis, lesions were made up to the dorsum sella laterally with a 45° angled stylet;

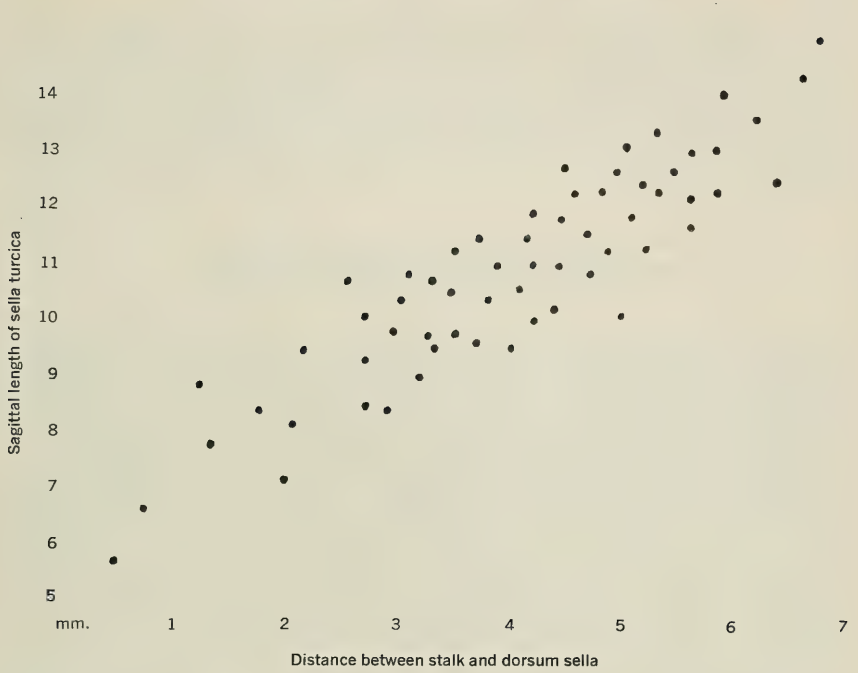

TABLE 1.—*Correlate of length of sella turcica to distance between anterior edge of pituitary stalk and the dorsum sella*

whereas in the midline, a 1- to 2-millimeter shelf of tissue was spared in the posterior midline to leave some intact pars nervosa.

Measurements of the distance of the oculomotor nerve to the midline and to the edge of the pituitary revealed a wide variability (from 10 to 19 millimeters from the midline). It was observed, however, that the nerve did not approach closer than 2.5 millimeters to the posterolateral edge of the pituitary. In this area, the oculomotor nerve is usually free in the subarachnoid space as it courses forward around the lateral wall of the dorsum sella before entering the cavernous sinus lateral to the internal carotid artery. The diaphragma sellae in this area is always intact and should prevent penetration of blunt instruments passing upward out of the hypophysis. It cannot, of course, prevent extension of some destructive agents such as radiation or freezing temperatures, although the circulation of fluid in the subarachnoid space and blood in the cavernous sinus and internal carotid artery should easily dissipate heat.

In summary, the anatomic study of the sella demonstrated some useful relationships of the substructures of the hypophysis to one another and to the radiographic appearance of the sella. It also demonstrated the absence of reliable landmarks for the height of the pituitary or for the sagittal length of the pituitary.

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To overcome this, the design of the RF electrode was modified to permit palpation of the capsule of the pituitary and the diaphragma sellae. This simple tactic, together with the usable radiographic landmarks, offered a more direct estimation of the spatial orientation of the pituitary.

STEREOTAXIC TECHNIQUE

Under general endotracheal anesthesia, the Talairach stereotaxic hypophysectomy frame [1] was fixed securely to the patient's head with external ear plugs and skull pads. Teleradiographs were taken in the sagittal and coronal planes. The target point of the electrode carrier was then adjusted to coincide with the midline of the anterior wall of the sella, 2 or 3 millimeters above its floor. With continuous X-ray guidance, a cannula was passed through a 3.0-millimeter drill hole in the floor of the sphenoid sinus to the anterior wall of the sella. The sphenoid sinus was irrigated with bacitracin solution. A 2.2-millimeter twist drill hole was made in the anterior wall of the sella. The insertion of the 2.0-millimeter RF electrode into the sella turcica to a predetermined depth depended on the calculated position of the stalk and diaphragma. The RF electrode was a hollow 2-millimeter insulated stainless steel cannula with a 5-millimeter uninsulated tip. A side hole at the tip of the cannula permitted lateral projection of a spring stylet to a maximum distance of 10 millimeters. With the cannula in position, the spring stylet was extruded in lateral, superior and inferior positions to permit palpation of the capsule of the pituitary, lateral of the floor of the sella below and of the diaphragma sellae above. The tactile sense gained from this maneuver permitted accurate estimation of position of these limits of the gland. Overlapping radial RF lesions were made by projecting the lateral spring stylets at various angles around the main axis of the electrode. The capsule of the gland limited the length of projection. To minimize diabetes insipidus, the medial posterior-superior sector of the sella turcica was spared. All lesions were made with Radionics Type 3 radiofrequency generator.[2] All lesions were made with generator outputs adjusted to reach the boiling point in 2 to 4 minutes. The end point was signified by a rise in tissue resistance as the boiling point was reached. Depending on the shape of the sella, six to 10 lesions were usually sufficient. Following removal

[1] Type II Hypophysectomy Frame. Alexandre et Cie, Romainville, France.
[2] Radionics, Inc., Burlington, Mass.

of the radiofrequency electrode, a silicone rubber dumbbell plug was forced into the anterior wall of the sella. The plug contained silver to provide radio-opacity. The sphenoid sinus was then washed with antibiotic solution, and short nasal pack was placed in the appropriate nostril. The duration of operation was from 50 to 90 minutes.

RESULTS

The method of endocrinologic evaluation, the endocrine results and the effects on diabetic retinopathy are discussed in a companion paper (*11*). Other pertinent results of this procedure are presented below. A total of 65 patients underwent radiofrequency hypophysectomy in the manner described above for diabetic retinopathy. Panhypopituitarism was produced in all but two cases. In the first, incomplete ablation resulted when the patient (H. S.) became hypotensive and diaphoretic before completion of the radiofrequency lesions, which conditions made it necessary to terminate the procedure. Later testing failed to demonstrate hypopituitarism. (Nonetheless the patient's visual disturbance was arrested and has remained so ever since (4 years)). In a second patient (B. C.) panhypopituitarism appeared to be minimal, although demonstrable. Panhypopituitarism was evident in all other cases. Although diabetes insipidus appeared transiently in most patients, only one required treatment on a long-term basis.

COMPLICATIONS

Although temperatures up to boiling were used in all but the first few cases, no damage to oculomotor or optic nerves, optic chiasm, or hypothalamus was apparent. In the first 11 patients, no effort was made to seal the puncture in the anterior wall of the sella. Three cases of cerebrospinal fluid rhinorrhea occurred but subsided with treatment, and in a fourth, meningitis and death occurred without prior rhinorrhea, 6 months after operation. Autopsy revealed total hypophysectomy (fig. 5). In the succeeding 54 patients, the punctures were occluded either with muscle tampons or with silicone plugs, as described above (*8*). In these patients, one instance of cerebrospinal fluid rhinorrhea was noted, and this was corrected with a muscle plug the next day. In a second patient, an improperly positioned silicone plug was replaced.

DISCUSSION

The safety of applying extensive heat within the confines of the sella turcica probably depends on the barrier to heat transfer that is provided by the carotid artery, the cavernous sinuses laterally and the chiasmatic cistern above. Anterior or posterior and inferior to the hypophysis, there are no important structures susceptible to a heat lesion. Laterally, however, the oculomotor nerves, and superiorly, the hypothalamus, optic nerves, and optic chiasm would be exposed to heat, were it not for the ready and efficient source of heat dissipation provided by these vessels and the cistern. Thus, it has been possible to apply adequate heat lesions to insure destruction of the gland without incurring visual disturbance. A similar natural safeguard such as is provided by this fluid barrier does not exist for other intrasellar destructive agents. Ytrrium-90 radiation is not confined to the hypophysis; consequently, visual disturbances are not uncommon, and cerebrospinal fluid rhinorrhea, due to radiation necrosis of the floor, has been a constant problem (*2*, *3*, *4*, *5*).

With cryohypophysectomy Rand (*12*) has experienced minimal cerebrospinal fluid rhinorrhea, but Wilson (*13*) noted this complication in one-third of his patients. In addition, it is not certain that the fluid barrier is as effective for cold dissipation since transient ocular palsies and visual field disturbances have been noted during operation under local anesthesia and have necessitated premature termination of pituitary ablation in some cases.

The surmounting of the problem of cerebrospinal fluid rhinorrhea was an important milestone for the radiofrequency method, for, in other respects, the latter was a satisfactory, effective, and simple procedure. Occlusion of the midline puncture with a muscle or synthetic plug probably obliterated any communication with extensions of the sub-arachnoid space into the anterior sella through a perforate diaphragma sellae.

TABLE 2.—*Effect on cerebrospinal fluid rhinorrhea of occluding midline sellar puncture with muscle or synthetic plug*

	Patients without sellar tampon	Patients with sellar tampon
Patients	11	[1] 54
Rhinorrhea	[2] 4	1
Operative death	[3] 1	0

[1] First 16 cases occluded with muscle; remaining 38 occluded with synthetic plug.
[2] Including presumptive case of rhinorrhea in patient who died of meningitis.
[3] Meningitis.

In closing, it may be concluded that the clinical experience with radiofrequency hypophysectomy supports its use as an easily tolerated procedure that sacrifices neither safety nor effectiveness in the quest for simplicity.

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CHAPTER 32

Summary of Papers on Ocular Aspects of Pituitary Ablation

J. WALLACE McMEEL, M.D.

For this symposium, 11 groups of physicians contributed data regarding their treatment of diabetic retinopathy by pituitary ablation. Among these groups every method of pituitary ablation has been used. The summary of data in these 11 series is directed to three areas:

(1) Ophthalmic criteria for selection of patients for pituitary ablation.

(2) The features of retinopathy that respond to pituitary ablation.

(3) Visual results following pituitary ablation.

CRITERIA

Although the data regarding the ophthalmic criteria for selecting patients for pituitary ablation varied widely, most groups adhered to certain basic criteria. Representative of these ocular requirements were four series (Kjellberg, ch. 33; Sweet, ch. 20 and 30; Zervas, ch. 31; and Rand, ch. 29) that totaled 345 patients. They were most similar, because the ophthalmologists or internists had once worked together in evaluating the ocular status of prospective pituitary ablation patients.

These groups had two criteria as prerequisites before doing pituitary ablation. The first was the presence of macular function in at least one eye (vision better than 20/200). The second was a progressive angiopathic retinopathy that could be documented. To ascertain the latter, all the patients were studied two or more times before having pituitary ablation recommended. Although most cases had proliferative angiopathy, a few cases consistent with "background retinopathy" in the O'Hare Classification [1] were treated. In these cases the central vision was deteriorating due to severe retinal edema and hemorrhage. In most of the 345, the threat of blindness was felt to be imminent within a few months.

Exudates alone were not considered an indication for pituitary ablation. Fibrous proliferation was frequently felt to be a contraindication to pituitary ablation, as it not only failed to respond to treatment, but often produced secondary retinal detachment that would profoundly

[1] O'Hare Classification, p. XXI.

decrease vision. If this fibrous proliferation extended greater than an arc of 180° about the posterior pole or if it were primarily fibrotic with only a few wisps of vessels, pituitary ablation was much less likely to be performed.

In three of these four series, documentation of retinal change was made primarily by mapping the fundus, using binocular indirect ophthalmoscopy for visualization. With this method, new vessels or fibrous proliferative changes were visible that might not have been well recorded by fundus photography, such as in the peripheral fundus, in the vitreous cavity anterior to the plane of the retina, and in eyes with a slight to moderate haze in their media. Direct ophthalmoscopy was used when greater magnification was required. In the fourth group fundus photography was the main method of recording fundus changes.

Although the other seven groups were diverse in many ways, the same two basic criteria for treatment noted in the above four groups recurred independently in most of the seven.

The Hammersmith group (ch. 27) required vision of 20/80 or better in at least one eye unless hazy media or other unrelated retinal disease had lowered the visual acuity. Also, proliferative retinopathy could not be a threat to the macula. Serial photographs documented the progression of the retinopathy. Classification of retinopathy was made by comparing the patient's fundus photographs with those of a set of standard retinopathy lesions.

Despite efforts to have at least one macula intact, most groups reporting the preoperative vision had some patients that did not meet this criterion. With the data available, only the Johns Hopkins series (ch. 47) and Dr. Lundbaek's series (ch. 25) did not allow treatment of any cases with vision 20/200 or less in both eyes.

The extent of maximum allowable proliferative retinopathy varied considerably in the different series. Most considered fibrotic proliferation that extended over an arc of greater than 180° about the posterior pole reason enough to refuse pituitary ablation. A lesser degree of fibrosis would contraindicate treatment if it were particularly dense, close to the macula, or producing a secondary retinal detachment. The Hammersmith group appropriately referred to these as irreversible changes, and denied treatment to these patients. The Johns Hopkins group did not treat patients with retinopathy worse than N_1 F_1 H_1 (O'Hare classification). Dr. Ray also did not treat any patients with significant proliferation (ch. 21). In Dr. Hardy's series (ch. 22) five of 30 patients had N_0 F_0 (O'Hare classification). By contrast Lundbaek's group had as one of its criteria that there should be proliferation with "gliosis" in at least one eye. In the 272 patients treated by Sweet

and Kjellberg, only one had purely background retinopathy (B—O'Hare classification) in both eyes.

In five of 11 series we have data regarding the number of cases that had N_2 F_2 (O'Hare classification) retinopathy in both eyes. Dr. Sweet's series had the highest incidence in this category—59 of the 92 cases with adequate data. Four other series show data indicating that they treated patients with the N_2 F_2 classification in both eyes.

FEATURES RESPONDING

With regard to the features of retinopathy responding to pituitary ablation, there is a striking unanimity in the data of every series showing that the angiopathic aspect of the retinopathy responded well to pituitary ablation. Also, exudates were not significantly altered, and fibrous proliferation progressed in many instances despite the "drying up" of the vascular and hemorrhagic lesions. Several series noted that intraretinal hemorrhages respond most readily to ablation, with new vessels requiring a more complete decrease in pituitary function, and dilated, segmented veins being the most resistant to change following advent of hypopituitarism. Dr. Balidimos' fluorescein studies show amelioration of neovascularization after pituitary ablation (ch. 16). A clearing of media has been noted by most groups also. Despite the above unanimity, opinions regarding the response of the retinopathy to total ablation versus incomplete ablation apparently have differed in the various studies.

The Hammersmith group stated that total pituitary ablation was most important in obtaining optimal results. The studies indicated that angiopathy ameliorated more rapidly and completely with total, immediate ablation.

Another viewpoint was expressed by the Kjellberg, Joslin, and Zervas groups. They felt that there was not a significant difference in the visual results of patients with a "moderate" degree of pituitary ablation and those with total ablation. However, in Kjellberg's series there was a lower success rate among patients with only a slight decrease in pituitary function or a delayed decrease in pituitary function.

VISUAL RESULTS

The visual results are the ultimate test of our skill in evaluating and treating patients with diabetic retinopathy. The results were surprisingly consistent and most encouraging. Table I shows the results of the 11 series. No patient followed for less than 6 months was counted unless he appeared as a failure.

TABLE I.—*Results of pituitary ablation*

[BPPI=Bragg peak proton irradiation; HSS=Hypophyseal stalk section; Hx=Hypophysectomy; Hx-RF=Hypophysectomy-Radiofrequency; Hx-Cryo=Hypophysectomy-Cryo probe; Y^{90}=Yttrium-90 irradiation]

Group	Mode of therapy	Number of patients	Arrest	Percent	Progression	Percent
Kjellberg	BPPI	152	84	64	49	36
Sweet	HSS	120	72	70	31	30
Hammersmith	Y^{90}	89		+0.37±0.23		
Joslin	Hx HSS	87	52	70	22	30
Ray	Y^{90}	22	12	75	4	25
	Hx	56	37	79	10	21
Pearson	Hx Y^{90}	20 32	30	65	16	35
Zervas	Hx-RF	42	38	88	4	12
Rand	Hx-Cryo	31	14	74	5	26
Hardy	Hx	30	15	68	7	32
Johns Hopkins	Hx	12	10	83	2	17
Lundbaek	Hx	15	13	87	2	13

Two series specifically avoided patients with significant proliferative disease (Dr. Ray and the Johns Hopkins group). Their success rate is slightly higher than several other groups. However, five groups had data on patients in the N_2 F_2 classification, and all had a success rate of 60 percent or better for these N_2 F_2 patients. In Dr. Sweet's series, the patients whose retinopathy was not yet N_2 F_2 had a success rate of 86 percent. In the N_2 F_2 group the success rate was 67 percent. Therefore, the presence of a moderate amount of angiopathic retinopathy should not deter one from doing pituitary ablation.

The proton beam irradiation has been successful in over 60 percent of the patients. This has been gratifying, as most of these patients would have been denied treatment by the prevailing surgical methods of pituitary ablation. Also of interest are Mr. Koehler's charts (ch. 57). In addition to showing the overall prognosis for each group on which there was data, the chart showing visual acuity at time of treatment reveals the less the level of the visual acuity in the group, the less well they did after treatment.

Several authors note the use of photocoagulation in conjunction with pituitary ablation, usually to obliterate nests of persisting new vessels or sites of recurrent bleeding. Most of these work out very well. In those personally treated, the photocoagulation has been directly applied to the involved area and not to a peripheral or central area of the retina remote from the new vessels.

Failures have most often been due to extensive vitreous hemorrhages or to progression of the fibrotic proliferative retinopathy, which produce retinal detachment or a fibrotic preretinal membrane. Some of these failures occur after 3 or 4 years of quiescent retinopathy. The cause of the resurgence of fibrotic or angiopathic activity after a long-dormant period is unknown, as there is no commensurate increase in pituitary function.

CONCLUSIONS

The data supplied to this symposium show that one may halt the ravages of diabetic retinopathy in a majority of the limited number of cases who meet the criteria for pituitary ablation. Physicians of this symposium are in general agreement regarding these criteria for treatment. Progress has been made in the past several years, as demonstrated by Mr. Koehler's statistical charts (ch. 57), which show that the newer and more innocuous methods of pituitary ablation appear to have the same success rates as the more established procedures. Although further progress in the treatment of diabetic retinopathy will hopefully alleviate the necessity for pituitary ablation, it still has a place in the treatment of this disease.

Discussion of Ocular Aspects of Pituitary Ablation

BERNARD BECKER, M.D., *Moderator*

Dr. Becker: We ought to ask the following questions: What does hypophysectomy do to the retina and what does it do to the eye? Does anyone have data as to the effects of hypophysectomy on blood flow? Is it increased or decreased? Do we have measurements of this sort? We emphasized earlier that there might be a reduction in blood flow as an early finding in retinopathy. Is this, in fact, altered? Is the first change seen, then, the change in permability that Dr. Balodimos finds? Is this the very first change one sees after hypophysectomy? What is the earliest that you see a measurable change in permability to fluorescein after hypophysectomy?

Dr. Balodimos: A few weeks. The leakage was not stopped within 1 or 2 weeks.

Dr. Kohner: We have started doing transit times in the retina. We measure mean circulation times for the arterial and venous phase before and after hypophysectomy. We have done this on two patients. Both of these patients had a markedly prolonged circulation time prior to yttrium implant. The followup was 3 months. By 3 months there was a marked reduction of mean transit time to within our normal range. This has nothing to do with volume flow, so we don't know whether the total flow to the retina has increased or not. All we can say is, blood goes through faster in the two patients studied.

As to changes in the capillary bed, the earliest changes are detectable at 10 days. We have not done photographs before 10 days.

In the completely ablated patients I quite often can see from the photographs taken at a fortnight that this patient probably has got complete ablation, because definite regression of new vessels and a definite decrease in leakage from microaneurysms is seen.

The most marked change in most microaneurysms and in small arterial abnormalities usually is seen within the first 3 months of pituitary surgery. There is further improvement later, but the rate of improvement decreases quite markedly. Small arterioles improve, capillary closure improves, microaneurysms improve, but in none of the

patients did we see complete return to normality. I think it's a very important point: we get much improvement but no return to complete normality (figs. 1 and 2).

Incidentally, this improvement in microaneurysms and hemorrhages occurs in all patients, irrespective of the degree of pituitary ablation. The greatest change, of course, would occur in the ones with maximum ablation. Following pituitary ablation in a number of patients who had small areas of capillary closure, capillaries are seen to function within a very short time, in 3 to 6 months.

I said yesterday the natural history of soft exudates in diabetic retinopathy is quite long. Following pituitary implant we feel we can shorten this considerably. Within 8 months in some patients all the areas of spots have disappeared. In some patients it was much more rapid (fig. 3).

Again I would point out that not only the spots disappear, but, on occasion, the area was revascularized.

FIGURE 1.—*From a color picture of an 18-year-old normotensive diabetic girl before pituitary ablation. Arrows (1 and 2) point at soft exudates. Arrow 3 points at relatively normal looking area.*

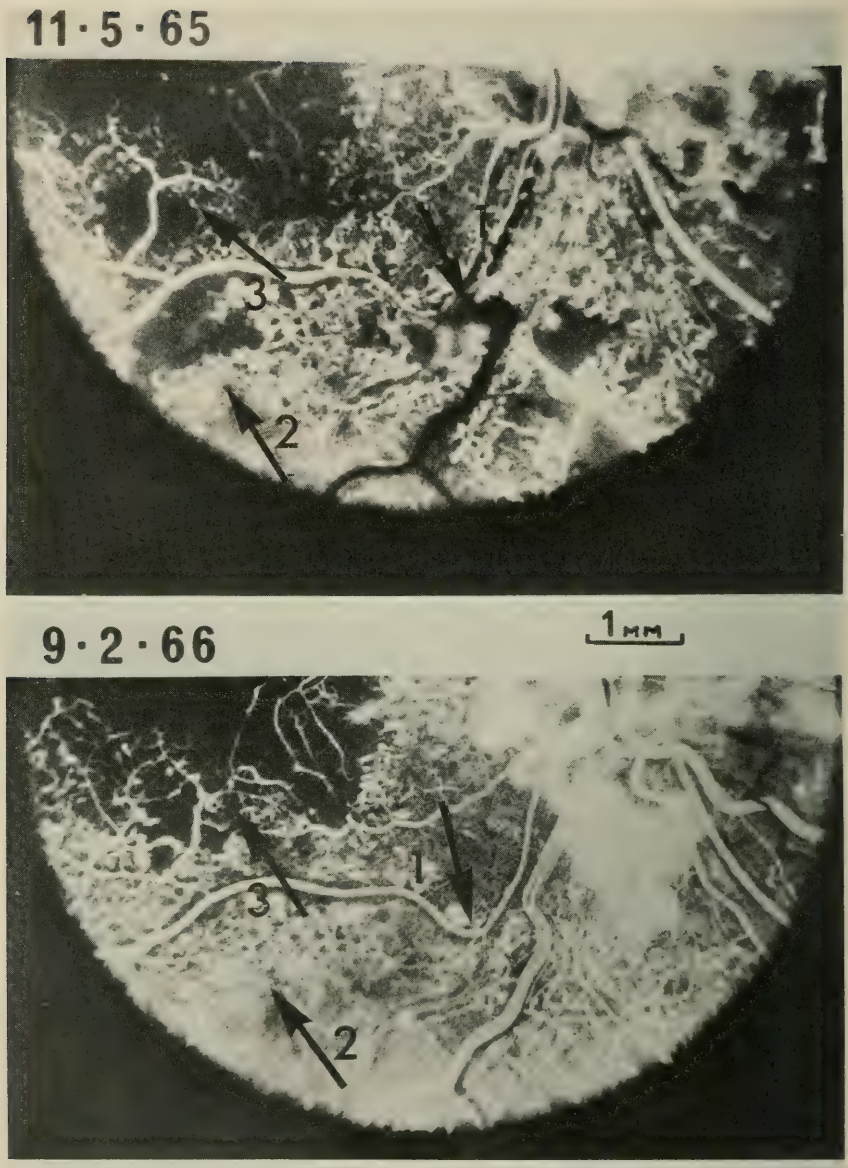

FIGURE 2.—*Fluorescence photograph of inferior temporal area of figure 1, Nov. 5, 1965, before yttrium-90 implantation of the pituitary and Sept. 2, 1966, 8 months later. Arrows 1 to 3 point at areas of capillary closure (1 and 2 were associated with soft exudates). Note perfusion of capillary bed following pituitary ablation.*

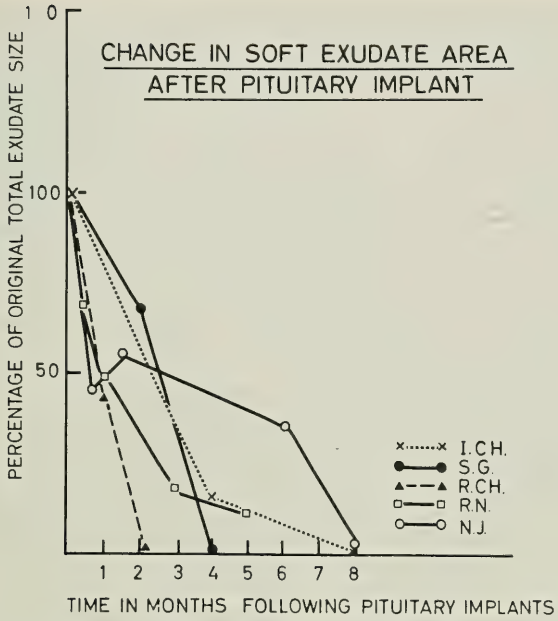

FIGURE 3.—*Change in soft exudate area following pituitary implant. Rapid improvement occurred.*

Large arteriolar abnormalities do not respond to pituitary implant. Microaneurysms respond, small capillary closures respond, small arterioles improve, but large arterioles don't (figs. 4 and 5).

Dr. Field: I would like to emphasize the rather constant occurrence of vitreous clearing within 48 to 72 hours after an abrupt, if you will, type of hypophysectomy. It is a fact that the patient appreciates; that the ophthalmologists making the examination appreciate; and it can be objectivated by reflectance studies as carried out by Dr. Ernst Wolf at the Massachusetts Eye & Ear Infirmary.

It is assumed or presumed that this represents decreased escape of proteinaceous and cellular material into the vitreous. If this is true, the type of thing Dr. Balodimos and everyone else can show (after a period of time, a decrease in leakage from new vessels) must begin very, very soon after the maneuvering against the pituitary has been carried out. I think this has a very strong implication as to what might be the mechanism through which the decrease in leakage is being achieved.

Dr. Becker: This is why I was trying to pin Dr. Balodimos down on when he sees this change. Hopefully, this would occur immediately, but he didn't imply that.

FIGURE 4.—*Fluorescence angiogram of right macular area before pituitary implant. Arrows point at abnormal arterioles.*

Dr. Norton: I want to ask Dr. Field something. From the publications, this is not a permanent change. In the course of a week, vitreous haze comes back again. At least this is what I have heard, and I wanted to know how you manage the patient postoperatively. If you leave the patient lying in bed for a period of 24 to 48 hours, you have no clear answers. This is how ophthalmologists try to clear the vitreous.

Dr. Field: I think this is something above and beyond that. While the stalk section patient remains abed for the better part of a week to 10 days, the patients who have been ablated by the radiofrequency technique are up the same day and are usually walking down the halls by the following day.

I would say that the prevalence and impressiveness of the clearing phenomenon within the first 48 hours has been greater, if anything, in

the radiofrequency series than in the stalk section series. It does reach some sort of a peak within 4 or 5 days, and then tends to be less impressive to the patient and to the observer approximately 2 weeks afterwards, but it is still better than it had been preoperatively. Perhaps Dr. McMeel would like to comment on this since he and Dr. Roth and others have all witnessed this, and have participated in the studies.

Dr. McMeel: In some of these patients, most of them, there was an adequate slit lamp examination just prior to the pituitary ablation, and, although many of them may have had some blood in the vitreous, there were also a large number that didn't have any blood in the vitreous. Thus, the clearing could not be associated with just a settling of blood.

FIGURE 5.—*Same as figure 4, but 2 years later. Complete ablation of pituitary. Note that while* (A_1) *remained unchanged,* (A_2) *and* (A_3) *progressed with occlusion of further side branches and development of large areas of capillary closure. Note also improvement in microaneurysms, a consistent finding after even partial pituitary ablation.*

Dr. Roth: I would like to backtrack a bit to this question of vitreous bleeding and clearing, which is a little bit unclear to me. Our patients are ambulated on the first postoperative day. When this vitreous clearing does happen it is quite dramatic, but it doesn't always happen.

Dr. Okun: Before people in the audience get the idea that vitreous hemorrhage can be cleared quite dramatically by any type of procedure, I think we have to know a little bit about the previous history of the vitreous hemorrhage.

Dr. Becker: Has anyone else done fluorescein studies in the early postoperative period?

Dr. Norton: We studied approximately 25 patients of Dr. Ray's. We had no preoperative comparison. These were all done anywhere from 1 to 10 years postoperatively. The only thing I can say is that they all leaked fluorescein considerably, even those that had hypophysectomy 10 years ago. I can't say they leaked more or less than they did preoperatively, because I don't have preoperative pictures, but I can say hypophysectomy didn't eliminate leakage of fluorescein from the retinal vessels.

Dr. Linfoot: One thing has impressed me. Following pituitary ablation, none of the changes that has been observed, at least as one sees them with the ophthalmoscope and fundus camera and so on, is distinct to hypophysectomy. In other words, all of the changes, as far as I am aware, have been observed to occur spontaneously. What we are dealing with following hypophysectomy is not a qualitative difference but a quantitative difference.

Since the neovascularization disappears more rapidly than one would expect, maybe we have accelerated the change from Mr. Dobree's classification of "type 2" to "type 3" following hypophysectomy. The question that I have to ask for those who have been doing fluorescein studies is, What happens to the fluorescein leak on the disc in cases after hypophysectomy and in those patients who have had spontaneous regression not associated with hypophysectomy. Does the same change take place or is there a specific difference? I see that Dr. Kohner is ready to jump. In the patients you followed, are there any changes that are specific in the fluorescein studies? I don't think the other changes necessarily are.

Dr. Kohner: New vessels do improve spontaneously at times. In my experience the very marked improvement Dr. Davis described and which Dr. Oakley described only occurs if the patient's diabetic control is extremely good—"very good" in our classification. We have seen this occur, not very often, but we have observed it. If new vessels improve, so does leakage.

Dr. Oakley: As an introduction to comments on the pituitary ablation series that were produced for this meeting, I was distressed to

find the lack of control data. It has been emphasized by several speakers now that qualitatively the changes can occur in untreated patients. I am not sure how hypophysectomy acts. I don't believe anyone knows. We believe it is important to control such patients after surgery as well as before. I think Dr. Lundbaek has the only series that has a proper degree of control. Dr. Lundbaek merely hasn't subjected his patients to an operative procedure. We have sufficient data to be able to compare patients who had what is almost a sham operation.

I think anybody working in this field must pay the utmost concern to experimental design. For instance, in the case of visual acuity, if you follow up all your eyes as opposed to treatable eyes only, you obscure significant differences and it is only in the latest followup of the treatable eyes that you get highly statistically significant differences between the maximal ablation group and the other groups. In the case of new vessels, there is a more obvious change. You see it in the other groups. I merely make these points now to emphasize the importance of experimental design of a control group and an accurate, objective method of followup.

Dr. Lundbaek: A month ago it was asked: What are the specific effects of hypophysectomy? I just want to point to one thing that would be interesting. Sometime ago we had a patient who was not a member of our experimental group, and one of the people working with me, Dr. Christensen, noted a severe abnormality of capillary fragility before ablation that was normalized after ablation. So we called in all our patients from our experimental series, and measured capillary fragility with the classical methods. Sure enough there was a striking difference. The patients who had been ablated had much less capillary fragility than the patients in the control group. The P value of that truth was less than 0.02.

Dr. Becker: You report that rubeosis improves in your hypophysectomized cases, and that less occurred than in the control series. The two questions I wanted to raise are: One, is there a general feeling that rubeosis improves after hypophysectomy? Second, if, in the control series, 16 of the 30 eyes have rubeosis, how does this compare with the experimental series as far as visual outcome and overall maintenance of function?

It seems to me the secondary glaucoma would so distort the data that one could not compare the controls and hypophysectomized cases.

Dr. Lundbaek: The things we call rubeosis in our work are very small changes that are very often not recorded. These are very slight changes that are just visible. Therefore, we have a very high incidence of rubeosis in all our patients. We record what we call primary rubeosis and not the rubeosis that is associated with glaucoma (secondary rubeosis). These patients don't have glaucoma. This secondary rube-

osis, which you see as a few big fat vessels, is not what we are speaking about. We are speaking about the tiny network close to the pupillary border. This is the thing we have seen disappearing after hypophysectomy. We have seen it disappearing without hypophysectomy but less often. During the time of observation, we have seen the development of glaucoma in five patients in the nonablated group and in none of the patients in the ablated group.

Dr. Becker: In your results are the glaucoma patients eliminated from the comparison?

Dr. Lundbaek: No.

Dr. Becker: Then if glaucoma develops, this would destroy vision. Thus, any comparison of vision would not be on the basis of the retinopathy, but more on the basis of other means of destroying retinal functions.

Dr. Lundbaek: That is right. But it is our fundamental idea that blindness is produced by a disease having an abnormality in the retina and in the iris.

The iris vascular changes are much more important than is usually recognized. We actually think this is just as important as retinopathy, and both should be evaluated in considering diabetic blindness. We are discussing the eye and not the retina.

Dr. Becker: I couldn't agree more. The reason I call this to everyone's attention is that yours is the only true control series. It is true that there is a group of controls built into the British series, but yours is a planned control series that came to the conclusion that there was no change in background retinopathy. The only significant difference was that the control group had more visual loss than the hypophysectomized, and that more visual loss could be accounted for not by the retinopathy per se, because it was the same in both groups, but by the glaucoma.

Dr. Lundbaek: Actually, as you have seen in our report, we have three parameters: visual acuity, appearence of the retina, and the visual field. Our impression is that all of the three changes are in the same direction. And on top of that we have the difference in glaucoma, so we think it is all of these things. We think today it might have something to do with capillary fragility.

Dr. Kjellberg: We have broken our cases down with respect to whether they improved in their vision, whether they were arrested, whether their vision was reduced short of blindness, or whether they were blind following proton beam therapy. I will only mention the extremes of these groups. In the groups that had actual improvement of vision, rubeosis was present preoperatively in 2 percent. In those that went totally blind, rubeosis was present preoperatively in 15 percent. With respect to glaucoma, 2 percent of those that improved had pre-

operative glaucoma. Twenty-five percent of those who went totally blind had preoperative glaucoma. These are as strong correlations as can be established preoperatively as to the visual outcome as any of the criteria by which we can try to estimate visual outcome other than retinopathy.

Dr. Becker: Has it been your experience that reducing pituitary function improves or avoids the development of rubeosis?

Dr. Kjellberg: I don't think we have really tried to work out data from that point of view.

Dr. McMeel: There were about three or four patients who had demonstrable rubeosis before stalk section. There was an amelioration in the rubeosis in these patients. One of them had a recurrence of pituitary function about a year or two after the stalk section. The rubeosis, which had improved, got worse along with the return of the pituitary function. This eye developed secondary glaucoma, and had to be enucleated. This is an anecdotal situation, but it is logical.

Dr. Davis: I would like to urge that, if we study rubeosis, we should all do gonioscopy, and not just study the vessels near the pupillary margin with the slit lamp. There certainly are changes one can see by gonioscopy that one would miss otherwise.

Dr. Becker: Fluorescein leaks out of these vessels. Anybody using fluorescein should be aware of this. Is this leakage altered by hypophysectomy?

Dr. Lundbaek: I would like to be able to tell you in 6 months.

Dr. Becker: It might be interesting to ask whether anyone had experience with the use of Benemid in patients with diabetic retinopathy. Some of you may not be aware that there is an active transport of fluorescein out of the eye. This transport system is inhibited in experimental animals by Benemid. There is good evidence that humans are similarly inhibited. I wonder if anyone has had the opportunity to have a patient with gout treated with Benemid, and has studied this patient either in terms of fluorescein permeability or in terms of progress of retinopathy. Is this within anyone's experience?

The question, of course, is whether this very prevalent transport system, the same one which transports para-aminohippurate in the kidney, is directly influenced in any way by diabetes or hypophysectomy, or whether we have merely a nonspecific type of leak greater than the patient can handle.

Dr. Kohner: In the last 3 years, I measured uric acid in 200 diabetics on at least two occasions. Apart from patients whose blood urea was over 70, I never found a raised uric acid even if the patients were hypertensive. Thus, my impression is that diabetics have, on the whole, a low uric acid.

Dr. Roth: I would like to say a word about three or four cases of patients with obvious rubeosis in one eye with glaucoma. None of these seem to have had an obvious change in the rubeosis following their pituitary surgery. One interesting aspect is that three of these patients had a great deal of pain in the eye with rubeosis. Almost immediately following surgery, the pain had resolved.

Dr. Becker: May I propose a question to you, Professor Lundbaek? If we are heading for some sort of hypothesis that altered permeability or bleeding tendencies are generalized, and that these are altered by hypophysectomy, why are the benefits of hypophysectomy confined to the eye? Why do these patients go on with renal and other diseases? Are these different blood vessels?

Dr. Lundbaek: I can only say that our experimental design would not allow us to find any change in any organ other than the eye. We have chosen our patients so they have a very severe and dangerous condition in their eye. The eye, so to speak, is on a brink. We are seeing them falling over the brink and are trying to compare ablated against nonablated patients as far as falling off the brink goes.

At the same time we are determined that the patient should have very little in the way of kidney or heart disease, so we couldn't expect any difference. In another 5 or 10 years this patient will, of course, be on another brink, on a kidney brink and heart brink and brain brink. Then, it is possible that we will see a difference. We would not expect to find any difference in this patient now.

Dr. Becker: Dr. Field pointed out that his patients' kidneys don't get better.

Dr. Lundbaek: I think it is very difficult to discuss anything when you don't have an experimental design. Five or 7 years ago, this special issue of Diabetes came out (Diabetes, vol. 11, November–December 1962), and our results were the same as everybody else's. It seemed as if there might be some effect, but we couldn't be certain. We said this was intolerable. There were only two things to do. Either jump off the wagon and quit, or make an experiment.

Dr. Kohner: Capillaries in other parts of the body, except perhaps the brain, leak fluorescein. This has been shown on electron microscopy. It is known that under normal circumstances every capillary in the body will leak fluorescein except the retinal vessels. I would ask Dr. Lundbaek: If you do permeability studies, would it be possible to get biopsies of the skin and look at these capillaries under the electron microscope? I am sure if there is any change that the change will be on the endothelial lining.

Dr. Lundbaek: Unfortunately, it is impossible to study the capillaries of the skin with electron microscopy. It is not feasible. It is

unmeasurable, unlike the kidney. Most of our function studies, as has been said, are insensitive, but we should try to develop some more sensitive ones. We have been working, for the time being, on dextran clearances. This gives some idea of the "porosity" of the filtering membrane by giving clearances of each molecular weight dextran species by itself.

Dr. Field: I would like to comment on the question about renal disease. Pathologists have had an opportunity to look at postoperative biopsies in approximately five cases. While the pathology of the eye is different from the kidney, it is their impression, on the criteria that they have established, that indeed there is "less activity" in the region of the hilar and prehilar vessels in regard to hyalinization.

Renal function tests are notoriously indiscriminate in giving sensitive data concerning what the histology in the kidney may look like. While it is not possible to prove a beneficial effect on the kidney, I don't think there has been anything brought forward that denies that such a possibility accompanies a hypophysectomy. There is some basis for this in histology, although it isn't absolutely convincing.

I think we are all familiar with the report of Ireland and his group (Ireland and others. Effect of pituitary ablation on the renal arteriolar and glomerular lesions in diabetes. Diabetes 16: 636–642, September 1967). The prognosis for renal disease is more difficult to extrapolate from past experience than is that for retinopathy, where at least we can make a daily or monthly examination with an ophthalmoscope.

Dr. Becker: Your mortality rate in the hypophysectomized group is the same or at least as great as in the nonhypophysectomized group. Since many of the deaths are renal deaths, there cannot have been great improvement in renal function.

Dr. Oakley: This number of renal deaths is, in fact, extraordinarily small. We had one renal death in 6 years of carrying out hypophysectomies. There was no rise in blood urea, despite the fact that the glomerular filtration rate is usually low after hypophysectomy.

One also should consider that the retina is not entirely comparable to the kidney. It has a high metabolic rate, and may be less dependent on glucose metabolism. I don't think that failure to demonstrate spectacular changes in the kidney in any way surprises us.

Dr. Kohner: When patients die of renal death, we don't know whether it was renal capillary death or renal arteriole death. I think it has been shown that arteriole disease does not improve after hypophysectomy. If the patients have already got renal arteriole involvement at the time of hypophysectomy, it can't be expected to im-

prove. It will progress. Patients get raised blood urea and hypertension in that way.

Dr. Greenberg: We have followed 18 patients with kidney functions before and after hypophysectomy by obtaining not only blood urea levels but also creatinine clearances, renal plasma flows, and glomerular filtrations. The majority of the patients showed a decrease in all of these parameters. This could be a nonspecific effect of hypophysectomy. We can't state that this simply means a progression of the diabetic lesions. In general, however, close to 80 percent of the patients showed a fall in all these parameters. I think this emphasizes that reasonably good renal function has to be an important criterion for hypophysectomy, because all parameters decrease afterwards.

Dr. Oakley: Our criterion is blood urea nitrogen of 38 milligrams percent. We had only one renal death over several years using this criterion, which was slightly higher than that used by some other workers.

Dr. Becker: It occurs to me that, in your hypophysectomized patients, you are using various forms of replacement therapy. It would seem likely to me that some of these would be given in excess, at least on some occasions. I have seen no reports, however, of any administration of hormonal replacement in excessive amounts leading to an exacerbation of retinopathy. Does anyone have any information on this?

Dr. Bradley: I think Dr. Field was the one who first mentioned having had the impression that some of their patients had flareups in retinopathy when thyroid replacement therapy was given. We have made the same observation, but have had no way of controlling this. This has happened enough times that we have continued to be slow about replacing thyroid until patients are really quite uncomfortable with their myxedema.

Dr. Peretz: In our group, two patients, after having total hypophysectomy, received growth hormone. In one patient, we had the impression the next day that there was a lightup in the vascular pattern of the retina with a hemorrhage. In another patient, approximately 4 weeks later, there was an onset of vitreous hemorrhages. These patients had been controlled and were doing well, one of them for a year and the other for two, so we think that this is a field for experimentation: replacing growth hormone after total hypophysectomy and seeing if you can revert the condition.

Dr. Schimek: We had a number of patients in the pituitary ablation series who developed a marked recurrence of their retinopathy, a florid angiopathy, 2, 3, or 4 years following the procedure. This is somewhat reminiscent of the rubeosis that recurred, or seemed to get worse, with

recurrent pituitary activity. Although this isn't related to giving too much hormone replacement therapy, it is a situation which, in most of our cases, we felt was related to a recurrence of pituitary activity. We have treated these with photocoagulation or laser coagulation.

I was curious to ask those who work with radiation therapy if anyone has had, 3 to 4 years after pituitary ablation, a recurrence of retinopathy with evidence of renewed pituitary activity? Has anyone then treated the pituitary with radiation?

Dr. Linfoot: We published one case which would give an answer to this question. There was a youngish girl in whom we obtained a partial degree of pituitary ablation and got a modest degree of measurable diabetic retinopathy response. We put in some more yttrium after a period of several months and increased the hypopituitarism as shown by function testing. The consequence of this was very dramatic: further increase in regression of the retinopathy.

Dr. Field: Although Dr. Bradley quotes my initial impressions quite correctly, we have, since that time, abandoned the withholding of thyroid. We give thyroid routinely, as soon as postoperative assessment has been completed (approximately 10 days afterwards). I frankly can't see any difference in the quality of responses. You are undoubtedly aware that large doses of testosterone have been recommended, and now one sees large doses of thyroid also being recommended with reports of good results.

We have had a patient who had had stalk section with subsequent displacement of the gold plate. Regrowth and reassociation of the hypothalamus with the pituitary was punctuated by a return of retinopathy. Hypophysectomy then produced a second amelioration of retinopathy. There is the older experience of, I think, Dr. Cooper in Rochester, who had a patient with total adrenalectomy. There was a primary response in retinopathy, but this recurred. He then did hypophysectomy, with a second dramatic cessation of retinopathic activity.

Dr. Peretz: We had two patients in that category. One who had an adrenalectomy who did well for a short period. He then had a total hypophysectomy, and this patient, if I recall correctly, is now still alive and doing well approximately 12 years after hypophysectomy. There is another patient who had proton beam irradiation who did well for a short period. He then came to New York and progressed, and we removed the pituitary. He did well for several years afterwards until his demise. So we feel total ablation of the pituitary is most helpful.

CHAPTER 33

Summary of Medical Aspects of Papers on Pituitary Ablation

ROBERT F. BRADLEY, M.D.

As long ago as the original work of Luft and Olivecrona (*1*), it was shown that renal function decreased following this procedure. The only other data I might add from a functional standpoint is that based on some work by Arthur Teuscher (*2*) who gave growth hormone to a small group of patients who had shown this diminution in renal function, and who reported a restoration of various functional parameters to preoperative levels.

As far as morphologic data are concerned, I think we are very limited in our information, thus far, to the report of Ireland (*3*), which, as many of you know, did show some change in the mesangial tissue toward normal. On the other hand, there was no significant alteration in the arteriolar lesion, which, if anything, was worse.

Dr. Field did allude to the possibly significant predictive value of hilar arteriolar changes in the kidney, and there was some correlation between the degree of these and a less favorable eye prognosis. We, and others who are reporting concerning these phenomena, didn't have any observations relative to this particular point.

The accompanying table shows the pituitary ablative procedures among the total of 895 reported to the symposium. (See appendices for data of individual authors.)

In our own experience and in the stalk section experience at the Massachusetts General Hospital, a patient ratio of two or more males to one female was noted. The was not borne out in the rest of the 15

TABLE 1.—*Pituitary ablative procedures—895 patients* [1]

Procedure	Number of patients	Procedure	Number of patients
Transsphenoidal Y^{90} pituitary implant	[2] 154	Transfrontal craniotomy stalk section	156
Transsphenoidal hypophysectomy	37	Subtotal hypophysectomy	13
Transsphenoidal selective anterior hypophysectomy	19	Hypophysectomy	128
Transsphenoidal cryohypophysectomy	31	Proton beam pituitary irradiation	152
Radiofrequency thermal hypophysectomy	42	Heavy particle irradiation	162
		Radioactive gold pituitary implantation	8
		Miscellaneous	4

[1] Male predominance for all procedures. In some series, ratio 2M:1F.
[2] 11 with 2 implants.

papers in the symposium which I tried to include, but there is, nonetheless, a very slight overall male predominance.

The characteristic age category of these patients is a 35-year-old individual with 20 years of diabetes, plus or minus. There are some variations in the series. In the series of Dr. Hardy (ch. 22) and Dr. Kjellberg (ch. 23), there is a wider age range and perhaps a slightly higher average age. The duration of diabetes also varied somewhat, being somewhat less in the series of Dr. Hardy. If one is dealing with an older age group, duration of diabetes will be incorrectly shorter in that the maturity onset diabetic patient often has an uncertain duration of diabetes, whereas one can determine with more precision when diabetes really began in juvenile onset case.

Regarding the general condition of the individual patients, it is apparent that there has been an effort on the part of each reporting group to select individuals for the procedure who are in reasonably good condition. Nonetheless, a number of patients included have had varying evidences of microangiopathy and/or atherosclerotic disease. A large percentage probably had neuropathy, at least of the peripheral type, although neuropathy has not been objectively evaluated in every patient.

The patients have been selected primarily on the basis of reasonably good renal function. Yet some have been included with elevated BUN's. The general criteria for accepting patients for pituitary ablation have been reasonably consistent in most of the reported series. The most significant exception is the series of Dr. Kjellberg reported from the Massachusetts General Hospital. These individuals were considered as surgically "unfit" for one reason or another, usually because of renal or cardiovascular disease (ch. 23).

The problems of intelligence and emotional adjustment of the patient have been emphasized by everyone. One may wonder about the adjustment in view of the fact there have been a few suicides reported.

The preoperative management of patients was comparable in most of the series as far as I could tell. For all procedures where pituitary ablation will be induced promptly, some soluble form of hydrocortisone or cortisone is usually given the day previous to surgery, and doses of 100 to 300 milligrams are given on the day of surgery. It is then rapidly tapered to the maintenance dose at the fifth to seventh day. Maintenance dose is usually 20 to 25 milligrams of cortisone or its equivalent in the morning and 10 to 12.5 milligrams in the evening.

Insulin programs have also varied. Some prefer to switch patients just to crystalline insulin in order to avoid the supposed dangers of using intermediate acting insulin. There is really little risk within a few days of surgery until one is tapering the doses of steroids, at which time patients rather abruptly become quite insulin sensitive.

Dilantin has been used primarily by those doing transfrontal craniotomy. The problems of hyponatremia and anemia a few days after surgery, associated with apparent water retention, have occurred in a few instances. Dr. Field (ch. 19) noted that his patients treated with radiofrequency had not had this particular phenomenon, which has been ascribed to inappropriate secretion of antidiuretic hormone.

Substitution therapy with thyroid, androgens, or estrogens has been started at varying intervals. Most observers appear not to start thyroid until there is some clinical evidence of a need for it, although Dr. Field currently starts thyroid right away.

Various devices for handling salt and water metabolism may become necessary in those having difficulty in the postoperative period with postural hypotension. This has been one of the problems we had in a few patients. Occasionally, liberal quantities of salt and small doses of 9-alpha-fluoro-hydrocortisone were needed.

Still later in the postoperative period, metabolic problems are related to the handling of insulin and adrenal steroids. Perhaps we don't communicate well enough with our patients, but I think we reported more episodes of adrenal cortical insufficiency, 22 in all, than did anybody else (ch. 17). Many of these were mild, it is true, but nonetheless the number was certainly sizable.

One of the points to be emphasized, perhaps even more importantly, is a need for the proper handling of insulin. Two of our worst episodes of hypoglycemia, which were nonfatal, occurred in individuals who had been given moderate doses of crystalline insulin at another institution. A real hazard is that someone not familiar with the presence of hypopituitarism in the individual might treat uncontrolled diabetes with usual doses of insulin. As was emphasized in several of the papers in this series, it is extremely important that these individuals have some sort of identifying card warning any physician seeing that person of the need to be careful with insulin and to use moderate to large doses of steroids during any acutely stressful illness.

As far as evaluation of the degree of ablation of the pituitary is concerned, most reports encompass the fall in insulin dose as a parameter along with cessation of menses. In this relatively young population, most of the females have been menstruating. In some the loss of urinary gonadotropins and/or alterations in vaginal cornification, and, in most, assessment of thyroid function have all been useful.

Unfortunately, no extensive data appear to be available concerning evaluation of adrenal steroid function except in the series from Hammersmith (ch. 27). There, withdrawal of steroids has been used as an indication; that is, if signs of hypoadrenocorticism appeared, the degree of ablation was considered to be complete or nearly so. It appears

to be known, or it has been suggested by earlier data, that plasma growth hormone and gonadotropin functions are those most easily eliminated when some degree of pituitary ablation is produced, whereas it is presumably more difficult to eliminate thyroid and adrenocortical stimulating functions, the latter perhaps requiring as little as 5 percent of functioning pituitary for persistence. Thus, I don't think we know for certain, in any of these cases, if absolutely total ablation was produced. Possible further data regarding this would be reports of individuals whose pituitary had been sectioned following death, but this would require many serial sections if one were to detect any small residual tissue. Apparently it takes only a small residuum of functioning tissue to produce significant hormonal activity.

Methods of evaluation of pituitary ablation would be greatly helped if we had more direct measurements, apart from those of growth hormone or ACTH (which are now available but with limited experience), for example of TSH. We are still restricted primarily to an evaluation of response of target glands. On the other hand, what is the importance of knowing this if, indeed, we don't really know what critical factor or combination of factors is being eliminated when we produce one or another degree of pituitary ablation? This question has been pointed out by earlier discussion and also by the fact that the various surgical methods for pituitary ablation produce moderate to nearly complete lasting ablation in the vast majority of patients. For comparison there are little control data or series of patients with incomplete pituitary ablation, except in the experience of Dr. Fraser's group, where lesser degrees of radiation induced demonstrably less hypopituitarism, and in the proton beam irradiated series of Dr. Kjellberg and Dr. Linfoot, where many patients had only partial pituitary ablation. In view of this, one wonders whether we really are measuring the right parameters. Should we actually not worry so much about this, and begin to look for other factors that are being altered when we produce varying degrees of pituitary ablation?

There are reasonable possibilities as to mechanism. Growth hormone has been talked about a great deal. Dr. Field has taken issue with this, based on data presented about 2 years ago (*4*). Although most of our own patients had little or no growth hormone response to insulin-induced hypoglycemia, some did have it, and yet, in some of the latter, maximal pituitary ablation was evident by other parameters. Failure to correlate eye response with changes in growth hormone's response to insulin-induced hypoglycemia, which was emphasized by the study at the Massachusetts General Hospital reported 2 years ago, has made it difficult to blame growth hormone, per se, for the effects on retinopathy. All the papers cite an occasional instance in which a patient

may have incomplete pituitary ablation, and yet the eyes do beautifully. Then, there is another patient where the pituitary appears to be completely ablated and one or more eyes do very poorly.

These experiences on both ends of the "bell curve" make it difficult to believe that we have really identified the exact factor. Is it total metabolic suppression that has something to do with changing retinal metabolism? Are there hydrostatic factors? Is there another factor of hypothalamic or pituitary origin related to retinal capillary permeability and pressure which is being altered? I don't know the answers.

I think this leaves the panel with more questions than I have answered. I must confess, having looked over the papers reporting incomplete pituitary ablation and noting what appeared to be rather good eye results, that I am not at the moment certain just what degree of pituitary ablation is necessary, although it looks at least as if more than a minimal ablation is required for the best results.

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Discussion of Medical Aspects of Pituitary Ablation

T. R. FRASER, M.D., F.R.C.P., *Moderator*

Dr. Fraser: There are, of course, many hormones that can be measured in assessing pituitary function. It is not only a question of measuring the level at any one instant but measuring the response to a stress test. We must, of course, also consider the practicability of measurement. It is not only what is the most relevant hormone, but also which of the various tests are reasonably practicable. It would be very helpful if we could have any agreement about what are the most suitable tests to assess the completeness of pituitary ablation.

Dr. Pearson: The tests of function in the past have been fairly simple for endocrinologists to do, and they certainly are useful. Of course, we now have direct measurements of pituitary hormones in blood. FSH, LH, growth hormone, TSH and ACTH. These are not all readily available at the moment, but certainly should become available in the not too distant future. I think that they will be an excellent indication of how complete the hypophysectomy is.

With some of these direct measurements, what happens is not quite so clearcut. FSH was thought to be knocked out very easily, for example, but may persist and be the only hormone found.

Growth hormone determination is now available commercially, and certainly is a "must" in evaluating pituitary function. Thyroid, adrenal, and gonadal functions, as we measured them in the past, are worthwhile. I think it is quite easy now to determine whether you get a complete or incomplete hypophysectomy. I suspect most of the ones in the past have been somewhat incomplete.

Dr. Fraser: You mentioned that growth hormone is relatively easily done now. Of course, it is very relevant how you measure it. In a normal subject it might be low at one moment and very high at the next moment. It is peculiarly difficult to measure in the diabetic because of the difficulty of inducing hypoglycemia, isn't it?

Dr. Pearson: There are standard provocative tests such as insulin-induced hypoglycemia. They are carried out preoperatively, and growth hormone is measurable. If the tests are done in the postop-

erative period and are not measurable, I think this is a reliable index of lack of function.

I would like to ask those who have measured growth hormone and those who had incomplete hypophysectomies whether there is a correlation between response and growth hormone levels. I must say I was not impressed by the Massachusetts General Hospital data that Dr. Bradley quoted as indicating that growth hormone doesn't play a role. I would not agree that that data showed it doesn't play a role.

Dr. Joplin: Although the numbers in our series are small, a tendency toward retinal deterioration is most evident in the patients whose growth hormones have persisted following pituitary destruction by yttrium.

Dr. Fraser: No conclusions can be drawn from Dr. Joplin's point that growth hormone is the factor relevant to the effect of the operation, but it is, perhaps a useful hormone to measure when assessing the completeness of your operative effect. If we keep our conclusion to that level, I think it is fairly safe.

Dr. Kjellberg: The business of growth hormone is confusing in the sense that its relevance is considered in a variety of settings of variable significance. Fasting and activity or tests to raise or lower the blood sugar are remote from the physiological circumstances of a person's diet and a person's activity. We have been interested in growth hormone not so much from the point of view of diabetics but relevant to acromegalics. We have 75 acromegalics, of whom about three-quarters are diabetic, but the frequency and relationship of retinopathy in this group are very difficult for me to draw any conclusions about. Thus, when we start talking about growth hormone, we are a long way from understanding what the growth hormone is like over a 24-hour period.

We should also have some reservations when we talk about growth hormone by realizing that we are speaking about the radioimmunoassay method. In the acromegalics, while all have elevations of radioimmunoassay-type growth hormone, the amount of the growth hormone and the evidence of somatic or metabolic suppression of acromegaly is often very poorly correlated. This has raised a question in my mind.

There is another factor of growth hormone that deserves consideration; namely, that which is called the sulphation factor growth hormone. When sulphation factor is evaluated with biological tests of growth hormone activity, it shows a relationship, whereas the growth hormone measured by radioimmunoassay has relatively little to do with the biological assay of growth hormone activities.

Dr. Fraser: Who has shown that sulphation factor correlates with features of acromegaly?

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Dr. Kjellberg: I will show you a reprint, not of my own, that shows a single case of acromegaly with a high sulphation factor growth hormone. It is inappropriate to draw a conclusion from one case, I realize, but nobody has studied acromegaly from the point of view particularly of this other kind of growth hormone. I am not making conclusions or suggesting conclusions about this other form of growth hormone other than to propose that we be open-minded about considering that this might be relevant.

Dr. Bradley: I am sure, if one were to measure growth hormone too soon after stalk section surgery, it is possible, since the levels might depress less readily than after hypophysectomy, that one might have confusing data. I ask this question, because, in Dr. Field's original paper, he mentioned a study period of up to 14 days, whereas in the paper prepared for this symposium, he measured hormones up to 6 months later. There was thus plenty of opportunity for stabilization of the person's metabolic condition.

I understand that, if a person is taking estrogen in any amount, this may increase the growth hormone response.

Dr. Fraser: Only to the protein stimuli, the amino acids.

Dr. Bradley: We have just begun to do arginine infusions. This might be a more reliable technique for assessing the response in view of the fact that it is often difficult to obtain a hypoglycemic stimulus which is sufficient to cause increased growth hormone output.

Dr. Fraser: It is extremely important how you induce adequate hypoglycemia. We have tested all our patients before pituitary ablation as well as after. Among those tested before, provided the initial fasting level is under 150 milligrams percent and they get 0.3 units per kilogram I.V., blood sugar drops below 50 milligrams percent. They all get a normal response. But this is not the case when you induce less hypoglycemia than that. What is popularly stated as adequate to drop to 50 milligrams percent in the blood sugar is quite inadequate in some cases. It's important to start from a fasting level of about 150 milligrams percent. That is an important point.

Dr. Field: There is hearty agreement with your proposition that it's very difficult in labile patients (who are dropping and raising their blood sugar all over the place) to get a smooth hypoglycemic test underway. It is helpful to give additional insulin or dextrose if required. The diabetic at this stage of his disease has frequent anomalous and peculiar responses both to the hypoglycemia and to hyperglycemia. They do not turn off the way they are supposed to. They do not turn on the way they are supposed to. Their turn-on may be delayed. In a limited experience the arginine provocation seems (1) much easier to conduct and (2) perhaps more reliable. The pyrogen

type of challenge is perhaps even more reliable than the arginine type of challenge, but it's considerably more devastating to the patient.

I might mention one other parameter I think we should be looking into: vasopressin. We know that vasopressin is highly influential on various membrane transport phenomena, toad bladders included. It is now becoming possible, although it is not at a stage of perfection, to conduct a radioimmunoassay for vasopressin. Here again is another one of the pituitary parameters that deserves attention.

Dr. Linfoot: We have seen patients who have had growth hormone obliterated by treatment, but who had adrenal and thyroid function that appeared to be normal and who continued to menstruate. The converse, in our experience, has not been true. If adrenal function was out, if gonadotropin function was out, if thyroid function was out, growth hormone was invariably out.

Dr. Fraser: I think we would agree with you on that.

Dr. Lundbaek: Another thing which can be done is to follow the variations of growth hormone. We are doing that now in normals and diabetics by measuring growth hormone every 30 minutes for 24 hours. The so-called inexplicable peaks are seen now and then, more often in diabetics than in nondiabetics. We have not examined this in relation to hypophysectomy, but that might be done. I wonder whether this is an academic question or a practical one.

Dr. Fraser: At the moment it is practical.

Dr. Lundbaek: Do we need such assessment? All of us try to do more or less complete operations (perhaps some people would not agree with that). We are trying to do a complete ablation. We then have a few relatively simple measurements to tell us if we succeed (such as appearance of clinical myxedema, cessation of menstruation, change in PBI, and change in steroids). I doubt we can ever come to the point of saying there is apituitarism, but, when we have simple results, we can say if there is any pituitary there. Then we have obtained the answer we wanted.

The other question, "How much of the pituitary do we have to take out to obtain this result?" is academic. Obtaining an answer to this is very difficult today.

Dr. Fraser: If, in addition to measuring growth hormone, one makes sure the insulin dosage has dropped significantly, and if one makes sure the menses have stopped, and if one makes sure to measure thyroid function, one has some useful parameters of what has been done to the pituitary. If you do not do those very simple and practicable tests, you are negligent, I think. Would you agree?

Dr. Lundbaek: Yes.

Dr. Bradley: We have a problem, and I noticed, in looking over Dr. Pearson's data (ch. 28, appendix F) that they too, I think, have one. They reported what may be autonomous thyroid function. We had a few patients who, by all other parameters, seemed to be completely ablated, but they had one out of three or two out of three thyroid function tests which were normal or became normal. I am concerned that the thyroid function assessment may not always indicate for certain that you have not ablated the pituitary.

Dr. Lundbaek: Did they develop clinical myxedema?

Dr. Bradley: There were some patients who, I would say, were borderline in that regard.

Dr. Fraser: We cannot call these patients completely ablated. Unless you can measure TSH and show it's scraping the bottom of the pit, they have some residual pituitary function.

Dr. Pearson: I think Dr. Bradley was referring to thyroids that function autonomously; take out the pituitary, and you do not influence them. We had a few patients who developed Graves' disease after a total hypophysectomy. We do not think this is a pituitary disease, anyway. If the thyroid function does not go down, then a suppression test with triiodothyronine is the test to be done. If you cannot suppress the thyroid with that, removal of the pituitary would not suppress it. Then, suppression is no longer a criterion of completeness of hypophysectomy. It is quite important to document as completely as possible the completeness of hypophysectomy. A lot of the bad results may be due to poor removal of the pituitary. I think it serves as an excellent check on the surgeon's technique as to whether or not he has accomplished total ablation of the gland.

Dr. Fraser: One of the questions to be answered is the suitable timing of the tests. Obviously with some operative procedures it can be done much easier than with others. Radiation may take a long time.

One of the points we should discuss is the hyponatremic syndrome that sometimes intervenes postoperatively, and which is often termed inappropriate ADH secretion. Is this a serious problem? How can it be avoided, and what is its cause?

Dr. Field: In the stalk section experience, it was a relatively common phenomenon, and duplicates, in a way, the appearance of diabetes insipidus following a stalk section in animals. An early period of diabetes insipidus, indicating ADH insufficiency, was followed, from the fifth to the tenth day after stalk section, by an antidiuretic phase. Finally, in a good percentage of the cases, a riproaring and more prolonged diabetes insipidus occurred. This can be avoided to a great extent by the relatively simple means of weighing the patient morning and night and by following the specific gravity of the urine. At the

fifth day, if you see your patient gain 4 or 5 pounds, the specific gravity, which will be 1.002 after subtracting the sugar, is now 1.022 or something like that. The time for withholding fluids and certainly for prohibiting the forcing of fluids has arrived.

Dr. Greenberg: Two things have helped in controlling this problem. We have adopted the attitude that we will not induce too rigid a control with antidiuretic hormone during the first 3 days following hypophysectomy. We have followed the urinary sodium excretion in a number of these patients, and found it to be tremendous. In a number of these patients, sodium replacement has been necessary. One of the possible reasons for this hyponatremia may be related to a fall in the aldosterone level. It is possible there is a fall in its level immediately after hypophysectomy to the point where they do not retain sodium. We gave them a good supply of cortisone, and eventually they recover from this. We have seen this happen in breast cancer patients who are hypophysectomized. Again, the majority, after a while, do not require any sort of replacement.

Part of the sodium loss may also be due to the fact that we are rather permissive in the control of the diabetes during the first few days following operation. We let them have a higher degree of glycosuria for fear of pushing them into insulin reaction. They may have an excessive amount of osmotic diuresis with loss of electrolytes.

Dr. Fraser: I would like to agree with Dr. Field that the control of the patient's weight and his water intake is practically enough to eliminate the problem.

It is true that with uncontrolled diabetes, patients will lose more salt as well. We studied the sodium balance in some of these patients very carefully, and the phenomenon is not explained primarily by loss of sodium. It's primarily a matter of water balance and inability to get rid of it.

Dr. Greenberg: I agree. If we decrease the amount of antidiuretic hormone replacement, we can, by and large, eliminate this problem in most cases.

Dr. Lundbaek: Do you mean to say there is a question of overtreatment? We have seen this phenomenon only when we have actually given the patients too much vasopressin. As to forcing fluid, we would never dream of that, because the patients can drink without our forcing them. They are thirsty. They drink what they need.

Dr. Fraser: Do you give them any replacement?

Dr. Lundbaek: Yes. After a few days, when we see it gets disagreeable for a patient to get up during the night and drink so many liters, we give them a bit, and ask them to regulate it.

Dr. Fraser: Inappropriate ADH secretion is not entirely attributable to treatment with ADH. In our cases it must be the irradiation effect. We do not give them posterior pituitary hormone at all, but occasionally the syndrome intervenes.

Dr. Bradley: In a few of our cases where this happened, they did not receive vasopressin. Thus, I don't believe that is the factor either.

We have studied one patient, and could not account for hyponatremia on the basis of total sodium losses. I think there is more to it than sodium loss.

Dr. Fraser: Yes. It's clearly very important to be careful of the patient's management both as regards diabetic control and as regards water balance if one is going to prevent serious hemorrhages in the eyes.

What are the relevant considerations in selecting a personality suitable for this procedure? Do we, in fact, see serious psychological disturbances after pituitary ablation?

Dr. Field: The fact that such patients are in a dire state of acute agitation, distress, and so forth, preoperatively seems simple enough to understand. Patients who have a good ocular result have a remarkably good response in their attitudes and emotional tone. Those who have poor responses have further deterioration of their emotional equilibrium. There seems to be no evident influence of hypophysectomy, per se, on emotional tone, provided adequate replacement is given.

Dr. Fraser: How do you select out the patient who is less likely to be careless, which is really the problem?

Dr. Bradley: We used psychiatric help when we were in doubt. The patients who may have fooled us the most were the hysterical females who might be tearing their hair and wildly decrying the problem they were faced with, but who, when the chips were down, did extremely well. The psychiatrist affirmed that the hysteric who managed to handle stresses previously in his or her life usually did handle something like this very well.

Concerning the correlation with success from a visual standpoint, I think Dr. Field's comment is generally true, but we had two notable exceptions of people who from a visual standpoint were very much improved, but who were obviously poorly chosen on our part. One instance was a girl who had a much too dependent relationship with her family. She subsequently fell apart because of changes within the family structure. The other was a young man who was not smart enough to recognize all the factors involved. He has deteriorated from an emotional standpoint postoperatively, even though his vision is good.

Dr. Lundbaek: After 5 years of looking at our series, we have two people in our control group and two people in our operated group who are not able to function as before.

Would someone comment on sexual function following hypophysectomy?

Dr. Greenberg: Impotence in males has been one of the major psychological problems after surgery. Many patients have had relative impotence before surgery and have adjusted to this. With androgen replacement we found that we could restore it (at least according to the patient) to the same level as before surgery, but in some of them, total impotence has occurred after a few years.

Dr. Fraser: Our experience does not agree with that.

Dr. Lundbaek: We have the same impression as Dr. Fraser. Most of the patients are not very good at sex to begin with. We have had several opportunities to notice that a patient was very sorry that the operation was done, because now he was getting totally impotent. However, we could look back in the records and show him the page where he said to us 2 years ago, "I am totally impotent."

Dr. Linfoot: There is one other side of the coin, particularly when you end up either intentionally, as we do most of the time, or inadvertently, as others do, with partial hypophysectomy. You have to caution the patient that the treatment you are giving him may be a poor contraceptive, and that he can not rely on the procedure to help him in that problem.

Dr. Lundbaek: After total removal of the hypophysis and after substitution with androgens, should the sexual function be normal or shouldn't it? Is it normal? Our experience is only from cancer and diabetic patients, where this question usually doesn't apply. Do we have any real knowledge about removing the pituitary in normal younger people? We don't know.

Dr. Fraser: It is not a very easy experiment to carry out.

Dr. Bradley: Our experience has been in patients with pretty normal function beforehand. As a group, they maintained reasonably good function. At least they were happy with it after operation. Any degree of loss preoperatively seemed to be associated with at least some loss postoperatively, in spite of replacement androgen therapy.

Dr. Greenberg: One man was studied after hypophysectomy while on androgens but not on any gonadotropic hormones. All parameters showed he didn't have any spermatogenesis. His potency was maintained with androgens, but I don't know how reliable his answers are.

Dr. Fraser: Both these comments and those on the neuropathy, which unfortunately we are rather ill equipped to comment about, indicate fairly clearly, I think, that there are some diabetic complica-

tions which are not having the same background as the retinopathy.

I would like to suggest that we give a little bit of attention, if we can, to the question of how does pituitary ablation beneficially influence the diabetic retinopathy. Now this, needless to say, is an extremely difficult question. Some of the effects of pituitary ablation will, of course, be on insulin production and insulin effect. We know the insulin dosages are reduced. Therefore, insulin is more effective. What other effects are there which are not attainable by what we commonly call blood sugar control? This is the point where the question of acromegaly is quite relevant. Do we get more diabetic retinopathy in acromegalics who get diabetes or don't we? I think the answer to that question is, nobody has a big enough series to know.

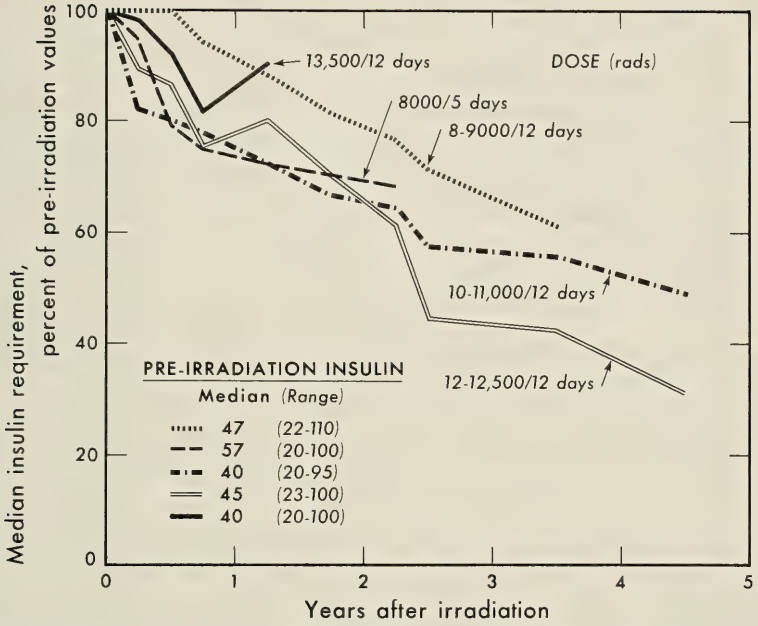
Dr. Kohner: I am not sure whether we know how many of these acromegalic diabetics will get retinopathy, but we know that acromegaly itself will not produce retinal abnormality. In 15 acromegalic patients studied with color and fluorescein photography before and after yttrium implant of the pituitary, there was no abnormality before and none after. It isn't enough to have abnormal levels of growth hormone. There is something more to it. Probably you have diabetes as well.

We were at a meeting in Glasgow where a paper was presented on biochemistry of the vitreous. It was found that the constitution of the vitreous in diabetes was abnormal. This researcher also did some work, I think, on two patients who had acromegaly. Their vitreous had a similar abnormality in their vitreous to that in diabetes. It was suggested that the vitreous abnormality may perhaps be related to growth hormone.

Dr. Fraser: There are some aspects of what might be called the blood sugar control of the diabetic that are a little different after pituitary ablation than in the unablated person. You must bear in mind that these might be important.

Dr. Bradley: The only change we noted in the behavior of response to insulin is that there are some patients who previously were sufficiently unstable that they required a splitting of their dose of intermediate acting insulin into a morning dose and a night dose. Subsequent to pituitary ablation, they seemed to get along fine with a single dose of intermediate type of insulin in the morning or with possibly a small amount of clear insulin.

Dr. Linfoot: In patients receiving suppressive heavy particle therapy, the change in insulin requirement after varying doses of heavy particles (with incompletely ablated glands) is shown in the following figure.



Chronological changes in insulin requirements following heavy particle pituitary irradiation.

When we decreased the amount of irradiation, we continued to see changes in insulin requirement. Initially, I thought that when we studied those in the lowest dose ranges, we could make some definite distinctions from the other patients. In the last 14 months I was able to evaluate a number of these patients who showed little or no change in target organ function save for a variable decline in insulin requirement.

Figure 3 in chapter 24 shows an example of an incompletely ablated gland showing both the insulin hypoglycemia and arginine tests before and at various times after treatment. The patient did not demonstrate changes in steroid or thyroid function until about 16 months after treatment. Similar studies were performed on juvenile diabetics (who were not on replacement therapy) and hospitalized for followup evaluation. I elected to do the arginine test.

Figure 6 in chapter 24 shows the change in insulin requirements in this group. The insulin requirements fell to about half of the pre-irradiation value. Lesser changes in adrenal and thyroid function were seen.

Figure 5 in chapter 24 shows the same type of study performed in a group of adult-type diabetics. Insulin sensitivity was measured as

the change in glucose disappearance rate ($t\frac{1}{2}$) in response to intravenous insulin. Shortening of the ($t\frac{1}{2}$) occurred in most of these patients following treatment.

Figure 4 in chapter 24 shows the results of the growth hormone (HGH) studies and compares normal responses to arginine and responses in untreated juvenile diabetics with retinopathy, the 26 treated juvenile diabetics, and the 11 adult-type patients. Interpretation of the responses in the latter group is difficult because obesity and other factors influence the HGH studies in this group.

All of the women in this series, with the exception of two, were still menstruating and only two patients subsequently required adrenal steroid replacement therapy, but all of them seem to have blunted HGH responses. These patients cannot be considered control subjects. The significance of these observations is not clear and a prospective study may help to clarify these findings. The therapeutic results of these patients are as good as we have seen in our completely ablated patients. I do not know what GH has to do with retinopathy. I do know that it seems to be consistently modified by treatment.

Dr. Fraser: What strikes me most obviously from Dr. Kjellberg's data is: if you don't drop the insulin requirement more than 30 percent (and we would regard that as no change), you don't have any patients with any benefit. This would imply that you have to do something to insulin dosage before you get an effect.

Dr. Kjellberg: I agree with that.

Dr. Simonsen: Yes. Centrifugal nerves have been demonstrated on the retinopathy couldn't be at least partially a consequence of degeneration below the stalk section as well as above the section, especially in the supraoptic nuclei of the hypothalamus. After all, Dr. Reimer Wolter from Michigan claimed that he found centrifugal or efferent nerve fibers from the area of the hypothalamus to the retina [1]. And, after all, the eye is developed from the hypothalamic area, and might eventually have connections with the hypothalamus.

Dr. Hardy: We were aware of this hypothesis about the centrifugal fibers from the hypothalamus. This is the reason why we have attempted selective ablation on the pituitary. I think it has been proven that pure anterior pituitary hormonal considerations could be eliminated from the physiological basis of retinopathy.

Dr. Bradley: I am not aware how to interpret this fact, since there was quite a bit of stalk manipulation in the selective anterior hypophysectomy cases. I can't be sure whether this point has been proved,

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[1] EDITORS' NOTE.—See Epilogue No. 4, references 18 and 19.

because there were quite a few patients with diabetes insipidus in the earlier procedures, were there not?

Dr. Hardy: Yes. But in order to prove this hypothesis, we have excluded all those cases who had the stalk manipulations.

Dr. Lundbaek: Can I ask whether this finding by Dr. Wolter, quoted over and over again, has been found by anybody else?

Dr. Simonsen: Yes. Centrifugal nerves have been demonstrated quite clearly, at least in birds and in chimpanzees or apes. One could say, even if these nerves had not been clearly shown in human beings, that they have been physiologically shown.

Dr. Davidoff: I would like to raise the possibility that experiments might be designed to dissect out more clearly the pituitary functions responsible for the effect on retinopathy. We already have in our hands the capability for doing what one might call selective chemical hypophysectomy by providing differential replacement therapy. Obviously, this is not easy to carry out, even on a long-term basis, or easy to document. With the advent of immunoassay and the availability of purified hormones and experience with replacement dosage, however, I would suggest we are derelict in our duty if we don't design this kind of experiment. Obviously, it would involve large numbers of patients and long periods of time, and one is dealing with threats to vision. It would clearly be a tricky thing to design. On the other hand, I would think that it might be feasible, and is something that we should consider.

Dr. Fraser: As to whether it is feasible, the normal procedure in a pituitary ablated subject is to put him on replacement therapy for the thyroid and for the adrenal cortex because they are available. But that isn't the same thing as if you hadn't taken away ACTH and TSH. You can't regard that as obliterating the effect of removing ACTH and TSH. The same applies to any other hormones you choose to replace.

Dr. Davidoff: I would think we don't have enough information on the effects, for instance, of replacing physiological doses of cortisone. If the dose is given with proper timing, such that one anticipates the 5-a.m. or 6-a.m. rise and prevents it, one should be eventually able to suppress in reasonable fashion the output of ACTH and the output of TSH. One should be able, by properly manipulating doses of steroids in patients with intact pituitaries to at least approach the situation in some of the moderate pituitary ablations.

Dr. Field: In regard to Dr. Davidoff's suggestion, there is, I think, in the University of Kansas a group who are trying every-other-day

dosages of exogenous adrenal steroids. They report, on a preliminary basis, some gratifying changes in eyegounds.

Dr. Packman: It was my impression that one purpose of this conference would be to establish some type of protocol or at least get our thoughts going so that we could compare the various series in terms of data available from patients already being treated. There is no consistency of data. It is very difficult to compare the series done in England with some of the series done in this country because of differing definitions, because of different degrees of pituitary ablation, and because of different studies that have been done to determine the pituitary ablation. Will it be of value to decide which procedure would decelerate the progress of retinopathy by setting up some type of prospective protocol with standard tests?

Dr. Davis: I certainly think we all agree with this. We hope, at least in the form of classification and in the form of some standard way of reporting visual results, to provide some standardization [1].

Dr. Sweet: I don't think we touched on one point in the conversations to date. We have made no effort to grapple with the question as to what parameter of pituitary function is being modified favorably in the patients that have had the various kinds of destructive procedures carried out on him. Clearly our objective, those of us working with that aspect of the problem, is not, in the last analysis, to find out what is the best way to destroy hypothalamic and pituitary function. Our problem is to find out what substance it is, or what balance of substances exists, that has become adversely modified, so that we can (for example, if we can identify the specific hormone in excess supply or the imbalance that has developed) come up with a far more specific treatment than anything we have heard about today.

If we can identify, for example, a hormone or a substance in excess supply, it is a comparatively simple matter these days to make an antibody to it. Hopefully, this would be an antibody that will prevent the hormone from exerting its deleterious effect. All of us in the room at the present time would be put out of business by this far more precise and far more specific kind of treatment (all of us except the ophthalmologists and internists, I guess).

Dr. Oakley: I think Dr. Sweet is putting forth an incorrect premise which is important to correct; that is, that there is an incorrect balance or an excess of the hormone which is being removed by pituitary ablation. It is much safer to say that we are modifying the cause of retinopathy by removing something, perhaps something that is present in a normal, physiological amount. You cannot extrapolate from

[1] EDITORS' NOTE.—See ch. 2.

the effect of an excessive hormone to the effect of removing a normal quantity of hormone. Similarly, you must not look for an abnormality in the pituitary function in the diabetic. We must merely look for the effect of removing what may be normal pituitary function. It is important to make this distinction.

Dr. Sweet: I accede to that, Dr. Oakley. I am referring to an excess for that particular patient; too much for that person in his particular pathophysiological state. There is no disagreement between us.

CHAPTER 34

Summary of Surgical Aspects of Papers on Pituitary Ablation

WILLIAM H. SWEET, M.D., D. Sc.

My review will begin with a summary of the techniques for achieving pituitary hypofunction and an indication of the degree and type of decreased function achieved by each method. To begin with the more thoroughgoing types of approach, I think we can be confident that the world's most experienced transfrontal total hypophysectomizer, our moderator, Dr. Ray (ch. 21), has removed from 98 to 100 percent of the entire gland in virtually everyone of his series of 56 patients. Fager (ch. 18), who has gone over to this type of operation in his last 41 patients, questions the totality of his removal in only five of them. Conversely, Pearson's group (ch. 28) has given up this procedure; they effected a total removal in seven of their nine patients.

Transsphenoidal open operations have been used in three groups of patients. In Lundbaek's series of 15 the oblique ethmoidosphenoidal approach of Hamburger and Norlen yielded suppression of thyroid, adrenal and gonadal function in every one of them (ch. 25). Pearson et al. have gone over to the microsurgical midline transnasal-transsphenoidal operation on their last 11 patients, and think total removal was achieved in all. Hardy (ch. 22), who devised this technique and route, has deliberately sought to preserve the stalk and posterior lobe in his 30 patients. In 19 the histologic examination revealed only anterior lobe and at most a few posterior lobe fibers; in the other 11 he removed posterior lobe as well.

In the other type of open operation, the pituitary stalk has been clipped or at most a bit of the gland at the zone of entry of the stalk has been removed. Fager cut the stalk near the diaphragma sella in 31 patients; he did this plus a little hypophyseal removal at the stalk in another 13. Dissatisfied with the reappearance of hypophyseal functions in these patients, he has, as mentioned above, gone over to total transfrontal hypophysectomy. Svien (*1*) has a series of 33 patients with stalk section, and we are reporting here (chs. 20 and 30) on our 121 such operations done from 2 to 9 years ago. In our patients the stalk has been clipped as high as feasible, often right at the tuber cinereum. Other clips and gold plate plus, more recently, gold foil have been interposed above the gland in an effort to hinder regeneration. Although the stalk-sectioned patients usually show panhypopituitarism

at first, we do not have late data on pituitary function in a significant number.

The stereotaxic transsphenoidal route has been used to introduce destructive agents. The pure beta-emitting isotope Yttrium-90 has been used in two 5 millicurie plugs, the A. P. M. Forrest technique, to destroy hopefully the entire gland. Ray's group gave this a trial in 22 patients, Pearson's in 20, and Rand (ch. 29) in an unspecified number. All three groups have abandoned it because of the complications and the incompleteness of hypophyseal destruction in some of the patients. However, Oakley, Joplin, Kohner, and Fraser (ch. 27), continuing to use this isotope for a total of 89 patients, have deliberately varied the radiation doses to give a complete spectrum of pituitary function from normal growth hormone and oxogenic steroid responses respectively to hypoglycemia and metapyrone up to the full pituitary suppression which usually occurs after 300,000 rads.

Roth and Rand have used, in 25 patients, a freezing probe 2.7 millimeters in diameter, which gives temperatures of −12° C. about 7 millimeters from the probe tip. They have sought to conserve some posterior lobe function. Anterior lobe functions were completely suppressed in 21, incompletely in two, and were borderline in two.

Zervas (ch. 31) has introduced a steel cannula 2 millimeters in diameter with an uninsulated tip 5 millimeters long. From a side hole a spring stylet can be projected to a maximum of 10 millimeters. Six to 10 overlapping lesions are made in such fashion as to spare some posterior lobe function. The tissue is boiled at each site by radiofrequency current. At the end of the procedure the site of penetration of the anterior sellar wall is plugged by a silicone rubber dumbbell made radio-opaque with silver. The method has yielded panhypopituitarism in all but two of the 65 patients thus treated.

Finally, precisely controlled beams of atomic nuclei have been fired through the pituitary region by Linfoot, Lawrence and colleagues (ch. 24), or controlled so that they would stop in the gland by Kjellberg and colleagues (ch. 23). Both groups, aiming their beams at the gland via multiple portals of entry at the scalp have concentrated the destruction in the gland. The Harvard group, using a single session of radiation have achieved a further concentration of the lethality by virtue of the fact that their proton beam passes through only half the width of the brain and gives up the huge increment of destructive energy at the end of its range, the so-called Bragg peak, right within the gland. The Berkeley group have treated 164 patients, mainly with alpha particles, in three divided doses. The massive doses they used at first were later reduced. Benefiting from the tremendous personally tendered aid from Dr. Lawrence and colleagues, we at Harvard have

used the 8,000- to 15,000-rad range, usually 12,000 rads, in 152 patients. The destructive effect takes months to approach its maximum, and each patient's endocrine status must be appraised serially for many months after treatment if glandular function is to be correlated with that of the eyes. In the Harvard series, 10 percent of the patients did not develop any measured suppression of pituitary function, and in a further percentage this effort developed too late to save vision. Thus, of 35 eyes with hemorrhages, this bleeding recurred and caused blindness in 12 before a hypopituitary state appeared. At Berkeley 37 patients were studied 1 to 8 years after an intrasellar dose of 8,000 to 15,000 rads which produced "a rather consistent fall in insulin requirements, a blunting of the growth hormone response to arginine with lesser effects on thyroid and adrenal function." In another of their patients given 17,000 rads to the pituitary, an autopsy 2 years later disclosed destruction of less than 25 percent of this gland as observed by light microscopy. Because of the greater biologic efficiency both of radiation at the Bragg peak and of delivery at a single dose, the lower standard dose in rads to the diabetics at Harvard may approach in destructive effect the 17,000 rads given that patient by the Berkeley technique. (Conversely, the dose evolving continuously for days from radioisotopic decay is rad for rad much less destructive than that given during minutes from the cyclotrons; hence the much greater total dose from isotopes required to achieve total destruction of the gland.)

THE NONOCULAR CRITERIA FOR SELECTION OF PATIENTS

The first two pioneers in the field, Olivecrona and Ray, and their immediate followers gradually came to realize that a patient with severe diabetic retinopathy was a distinctly worse risk for total hypophysectomy than a woman with advanced metastatic cancer of the breast, even though the diabetic might look superficially healthier. Both men experienced a mortality by 1 month after surgery of 20 percent of their first 20 patients.

Field began not just a new chapter, but rather, I would say, a new book on the subject when he insisted in 1959 on presenting surgeons with a much more favorable group of patients for the making of hypophyseal lesions. His criteria of potentially useful vision in at least one eye, associated with cardiovascular, renal and intellectual functions of stated degrees of acceptable impairement, have provided guidelines accepted since then with various shadings by most others working in this area. The additional criteria of Field and colleagues of

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documented recent progression of angiopathic and/or hemorrhagic retinopathy has mitigated against the performance of unnecessary surgery. Parenthetically, I may say that recognition of the dynamic factor of an abrupt downhill course in the retina has constituted the soundest basis for positive selection of patients, even though it may be difficult to classify in more precise terms.

In general, the total hypophysectomizers, e.g., Ray and Fager, have had the most rigid criteria; Ray, for example, accepting very few patients over 40 years of age and Fager placing 3 grams percent of serum albumin as the lower limit of acceptability for operation. Not much less rigid are the criteria of those of us doing stalk sections; e.g., we ourselves place the lower limit at 2.5 grams percent of serum albumin, and Svien's Mayo Clinic group are at least as rigid on the ophthalmic criteria as we are.

The standards of those using stereotaxic transsphenoidal methods are a major notch more liberal. Thus, 20 of the 32 patients on whom Pearson's group did Y^{90} implants and all of the 22 Y^{90} patients of Ray et al. were unfit for transfrontal operations by their guidelines concerning systemic disease. I should mention that Hardy has been able to do his microsurgical open operation via nose and sphenoid without mortality on patients with significant nephropathy and cardiovasculopathy, including hypertension. A possible exception to this liberality is Rand, who admitted only 31 of 200 patients with diabetic retinopathy for his stereotaxic cryohypophysectomy.

The users of protons and alpha particles, doing the least stressful procedure, have had the greatest freedom in patient selection. Thus, only one-sixth of Kjellberg's patients met our nonocular, systemic standards for stalk section. For example, 48 percent of Kjellberg's series had blood pressures higher than 160/100.

MORTALITY AND MORBIDITY

By adhering to the criteria they have set for themselves, each group with a large series has been able to keep the mortality of its procedure at a very low level. Thus, Ray has had no early postoperative deaths in his last 38 transfrontal hypophysectomies. Fager's lone death in 41 such patients was from a myocardial infarct during the second postoperative month. In his first series of 29 stalk sections there was one death from frontal lobe infarction and edema. In our 121 patients submitted to stalk section, there were three deaths during the first 3 postoperative months: one from myocardial ischemia; another from pulmonary embolism as a sequel of a low anterior spinal artery syn-

drome; and the third from pulmonary emboli in a man who had been at work for 4 weeks.

The major exceptions to this cheerful situation have been in those with Y^{90} implants at doses designed to destroy the gland. The problems encountered by Pearson et al., Roth, Rand et al. and Greenberg, Ray et al. have been described in earlier chapters. Hardy has added to these accounts in this volume the information that he has carried out these procedures in 44 cases, and has given it up because of unacceptable numbers of sequelae. Meningitis, especially late meningitis, with or without the warning of cerebrospinal fluid rhinorrhea, and hemorrhage from the radiation necrosis of arteries have killed enough patients and there has been so much nonlethal morbidity as well as uncertainty of destruction of the gland that this procedure has been abandoned by the Cornell, Case-Western Reserve, Montreal, and UCLA groups. Despite a bias in favor of the use of focal radiation procedures, I have concluded that it would be next to impossible to devise a technique of beta radiation which would destroy the pituitary gland early without later destroying some of the traumatized anterior sellar wall. The continuing use of this method by the group at Hammersmith, not only for 89 diabetics but also for hundreds of women with breast cancer, lead me to make the following special analysis of their data in the diabetics. They proceeded more critically than the other workers above cited in that they measured the sella turcica in radiographs, modifying the length of the Y^{90} rods and the radioactivity thereof in accordance with the hypophyseal topography of that individual. They have varied the radiation dose planned for the periphery of the gland, employing in their first 38 cases three dose ranges (*2*). Using their careful late studies of pituitary function, they classified the degree of hypopituitarism according to the criteria described in that article, achieving these results:

Radiation doses (rads)	300,000 r	100,000–200,000 r	50,000 r
Slight ablation	0	0	8
Moderate ablation	4	6	2
Maximal ablation	10	3	5

They comment that of the five in whom 50,000 rads yielded maximal ablation, this may have been due in two to further pituitary necrosis associated with meningitis. The inconsistency with which even 300,000 rads was followed by maximal ablation is evident from their table. Of the first 38 cases eight developed CSF rhinorrhea; this figure had risen to 18 by the time they had done 100 implantations in 89 cases (ch. 27). One of the patients in the first group died in a severe hypo-

glycemia episode during recovery from meningitis, and another died at 3 months of sinusitis and pneumococcal meningitis, never having had a recognized CSF leak. Another patient in the second group died of meningitis; six others in the whole group recovered from this complication. It would seem that even the greater care and vast experience of the Hammersmith group have not brought a complete solution to the problem of meningitis. The fact that the anterior sellar wall is so thin that it cannot be seen in sagittal radiographs of the sella turcica makes it impossible to detect increasing vulnerability to this complication as a small area of late radiation necrosis of bone appears. The other complications and deaths they describe remain the bane of all of us who are destroying pituitary function in diabetes.

Methods of destruction of the gland by radiofrequency heat, by cold probe and by direct transsphenoidal microsurgery would appear from the published data to be superior in terms of fewer sequelae, and have the additional advantage of an immediate destructive effect. As one reviews the data presented to us here, either the radiofrequency heating method of Zervas or the microsurgical approach of Hardy seems to me to offer the best tactic for a newcomer to learn in the management of these patients. There is in my view no longer any justification for the use of yttrium-90 for the purpose of total hypophysectomy. Moreover, this may not prove finally to be the proper goal in the treatment of diabetic retinopathy.

Regarding the morbidity of the various other procedures, I should emphasize only that the transfrontal operations appear to be significantly worse than the transsphenoidal stereotaxic or microsurgical approaches. Thus, after our 121 stalk sections the complications include 24 urinary tract infections, five wound infections, two fairly long-lasting temporal hemianopias in the better eye, five cerebral ischemic icti, and eight bilateral anosmias. Postural hypotension is a further complication of total hypophysectomy not seen after stalk section. The general stress of total transfrontal hypophysectomy is probably a bit greater than that of stalk section. Thus, Ray (*3*) says that the average stay in the hospital after the former operation is nearer a month than the mean of 18 days after our stalk sections. Ray estimates his incidence of bilateral anosmia at about 25 percent. Neither he nor Fager (*4*) have had any measured worsening of vision related to operative trauma. Because of early toxic reactions he has seen from Dilantin, Ray prefers phenobarbital for prophylaxis against seizures. These have not been a problem in his series, Fager's or mine. (In the latter two Dilantin has been used routinely.) Ray's few wound infections have been superficial with no cases of meningitis (*3*). Fager, using no sutures in temporal muscle or galea and leaving as an extra-

dural foreign body only a plastic dime button, has had no wound infection at all (*4*).

Although we have learned how to reduce strikingly our significant complications, the patients nevertheless require a tremendously vigilant, resourceful physician of the Richard Field type to control the fluid, electrolyte, and diabetic metabolic problems in the postoperative period. Such assiduity is apparently not so mandatory to avoid a steep rise in morbidity after the transsphenoidal procedures. Unless it can be demonstrated that stalk section exerts a specific (as yet undefined), favorable influence in this disorder without depriving the patient of all of his anterior lobe function, it should probably be abandoned in favor of the transsphenoidal approaches. One should at the same time point out that the vision of the patients with stalk sections is holding up so well over the long term that we have a special obligation to study this group intensively to try to find out why this has happened.

The least stressful procedures, the irradiations with protons or alpha particles, have been carried through with the lowest significant morbidity and with no direct mortality, despite the fact that the patient population includes those of highest risk. The only significant complication of the proton irradiations at the Bragg peak has been a nonpermanent extraocular muscle palsy in 23 percent of the 152 patients. This has been reduced from 40 percent in the first part of the series to 10 percent in the latter part, an improvement related to mapping by computer of isodose curves. The palsy appeared an average of 3 months after treatment and the complaint lasted an average of 12 months, ranging from 2 weeks to 27 months. There was a questionable injury to the optic chiasm in one patient. Diabetes insipidus of a degree requiring pitressin for 1 to 9 months appeared in six patients. The 37 Berkeley patients with a similar but biologically less effective dose in rads have experienced no mortality and little or no morbidity.

Until the long-term merit of the newer procedures is proven, neither Ray nor Fager doing total hypophysectomy, Joplin implanting Y^{90}, nor I doing stalk section is likely to give up lightly his hard won expertise in the method with which he has had so much experience. However, I think each of the four of us should now reexamine the advisability of continuing his method of treatment for this disorder.

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Discussion of Surgical Aspects of Pituitary Ablation

BRONSON RAY, M.D., *Moderator*

Dr. Ray: This meeting, from a practical standpoint, is concerned with the justification, or perhaps the desirability, of hypophysectomy in patients with diabetes. Secondly, it is concerned with whether the procedure of hypophysectomy must be complete.

From a scientific standpoint, we, of course, want to know how or why the procedure works, if indeed it does. I feel, with certain reservations, that the direction of this meeting thus far implies that most of us are willing to accept the fact that there is a place for hypophysectomy, that it does benefit retinopathy, but we still have reservations that are understandable. For example, very little has been said directly to this point, but we take it for granted that hypophysectomy is a palliative procedure. It hasn't cured anybody's retinopathy, much less diabetes itself. Therefore, we have the problem of determining a given patient whether a palliative procedure that carries certain unwanted risks is justifiable. We are not extending lives; at least no evidence has been brought to bear on this point thus far. We even question whether the vessels in the kidneys might undergo some benefit from removal of the pituitary.

Speaking from a surgeon's standpoint, we are interested in which patients stand the best chance for improvement. We certainly don't like to operate on a patient and have him come back and say "this was a useless job" or "I am crippled for life." We have to deal with that patient. We want to know in which patients the risk is unjustified or predictably is likely to be a failure, and also what is the most acceptable way or ways to accomplish hypophysectomy.

The members of the panel represent, in one way or another, eight distinct methods of destroying the pituitary.

Dr. Fager: Dr. Ray, as you said, hypophysectomy is a palliative operation, but no surgeon likes to do an operation that wouldn't prove to be worthwhile, and even in a palliative operation we would like to have a patient who will live 2 or 3 years. Therefore, I think it is extremely important, and I have always felt so, that our systemic

criteria include those patients who do not have severe renal and cardiac disease and certainly those patients who aren't going to die of a coronary within a matter of a few months. To preserve vision for just a matter of 6 months or a year, to my way of thinking, is not worthwhile.

Dr. Joplin: Quite clearly, Dr. Sweet has placed those who implant yttrium-90 on the defensive (ch. 34). Perhaps we might consider in a factual way the various items of morbidity which have been encountered by various other techniques in terms of whether or not they occur after yttrium-90 implantation also. First of all, Dr. Sweet drew attention to the fact that mortality is very low from all of the procedures reported today. In the yttrium-90 series, there was mortality in two patients that was attributable to the operation. Both were infections, and both occurred more than 5 years ago. Indeed, since the adoption of our current antibiotic policy, infection has been totally unknown.

Going down the various items of morbidity then, the question of diabetes insipidus is unknown after yttrium-90 implantation. It is unusual to require Pitressin for more than a day or two. Fits are unknown. One of the complications of yttrium-90 implantation, we were told, is necrosis of the floor of the pituitary fossa. This is something we have never seen with our technique, whether applied to diabetes or any other problem.

We have had no problems whatsoever from carotid artery hemorrhage. This is something quite unknown, although it was presented as a complication of the method. Ocular nerve necrosis has not been seen in the last 2,000 consecutive implantations, and neither have we any instance of optic nerve damage.

The only morbidity for us to consider is CSF leakage. The figure we reported to you for the series we are considering today was 18 out of a total of 100 consecutive operations on diabetics. That goes back to the first pituitary implant done in 1957 for this purpose. Now, we should consider what the No. 18 represents. Every patient who comes to see us after having an implant operation, who admits to having had a drip of water on the end of his nose, is recorded as a patient having a CSF leak. There is no way we can distinguish between the London wintry running nose and CSF leak, but, being physicians, we record any patient who thinks he had a running nose. In only three of the 18 have any more radical procedures been required to arrest the leak. These three were handled with muscle grafts. We now use our own plastic plugs for the arrest of these leaks. We only had three instances of CSF leakage in our hospital in the last few months, although we do four procedures every week. We have tried out a new plastic plugging technique, which was effective in two of these pa-

tients, and ineffective in one. We now are using this plastic plug technique for prophylactic obstruction of CSF leakage through the drill hole in the anterior wall. In addition to that, the old problem of poor fixation of the Yttrium has now been overcome by the attachment of a polypropylene extension.

I think we are now left with rather a different picture from that of Dr. Sweet's initial summary.

Dr. Sweet: I would ask a further question here of Drs. Joplin and Fraser. I referred specifically in my summary (ch. 34) to the problems that others seemed to have experienced with the type of dosage used to produce total hypophysectomy; mainly, 10 or more millicuries delivered into the substance of the gland. Have you broken down your morbidity series into those patients who had radiation of that order of magnitude and those others in whom you have deliberately sought to produce a partial destruction?

Dr. Joplin: The morbidy is obviously dose related, as it is with all these approaches. It is very difficult to talk of morbidity in a blanket sense, because, of course, techniques are being altered all the time. If we take the problem of breast cancer, where we routinely double the dose for total destruction of the normal pituitary, something like two breast cancer operations are done every week in our institution. We only had a total of three leaks in the whole institution in the last 9 months. During that time, quite a large number of patients had been treated with very much larger doses than we are using today in diabetes.

Dr. Ray: In all fairness it should be emphasized that Dr. Sweet was referring to predictable and sequential total ablation or removal of the gland. On that score he implied he found the methods of Drs. Joplin and Fraser wanting. But Dr. Joplin has answered his side of the question too.

Dr. Kjellberg: The proton method has been used in 170 procedures. I want to make it clear that we do not regard this as a choice procedure. In general, the cases coming to our hospital, if they are favorable candidates who are good physiologically and if their vision meets the criteria set up, have been given the priority of a stalk section. Our cases represent the rejects of stalk section. I think it is worthwhile considering selection from the point of view of what do you do with the cases who don't fit the criteria of the more formidable methods. The advantage of convenience in the proton method has the limitation of late onset of hypopituitarism, and vision may be lost for this reason.

Dr. Ray: Dr. Kjellberg, how often, in a patient treated by your method, have you then subjected the patient to surgical hypophy-

sectomy or stalk section if he showed progression of retinopathy to a dangerous degree before your method could have effect?

Dr. Kjellberg: I can't give you a very precise figure. Dr. Hardy mentioned that he has done one of my cases by his method. There have been a couple of others. I think there is one in the series of Dr. Field.

Dr. Bradley: I think we have three or four.

Dr. Kjellberg: Perhaps a half dozen have gone on to some other method.

Dr. Ray: Dr. Linfoot, is there a difference in the speed of effect between the proton beam that you have been employing and the Bragg peak effect?

Dr. Linfoot: Yes. I think it is important to point out that we use a through and through procedure covering the entire gland, anterior and posterior lobes. We fractionate the dose over an interval of 12 days in most patients. Dr. Kjellberg's group delivers the dose in one sitting, and uses the Bragg peak, which has the advantage of its stopping power. Our effect would be less, and would come on even less abruptly than Dr. Kjellberg's. On the other hand, I believe we cover our gland much more completely than they are able to do with their present stereotaxic apparatus.

Just a year or so ago, we changed the apertures, and found that we can no longer correlate changes in insulin requirement or endocrine change or anything else with the dose. Thus, a little change in technique with these heavy particles may make big changes in the effect that you get on the gland.

Dr. Zervas: I would like to ask Dr. Field a question, since he has been associated with three different methods of hypophysectomy, about patient selection. In particular, what do you consider the differential selectivity so far as proton beam and transsphenoidal procedures are concerned? Do you feel there are patients who don't qualify for transsphenoidal approaches who qualify for proton beam?

Dr. Field: One can approach patients who do not measure up to the qualifications for craniotomy by either the radiofrequency method or by the proton beam method. However, those who are in such dire straits as to make one hesitate with the transsphenoidal technique are probably unapproachable from the radiation point of view as well.

There were 11 patients who were treated with the radiofrequency technique prior to my arrival in Philadelphia, who are being studied primarily for the effect on renal disease. All had azotemia and some had rather profound uremia. If I summarize your report correctly, the actual operative intervention caused little or no difficulties either with medical management or the other factors involved in the procedure, so that this particular technique, from the three that I had

have opportunity to have experience with, is the one which combines best the elements of safety, simplicity, ease of management, and yet certainty and immediacy of effect.

There are very few patients who are not suitable for this approach who would be good material for an irradiation approach.

Dr. Fager: I rather feel that we can get a patient through an hypophysectomy just as easily as through any transsphenoidal procedure. The question then comes up as to which patient you should really select. If he is too far advanced for any of the surgical procedures, the chances are he may be too far advanced for anything.

Dr. Kjellberg: How do you reckon the cardiovascular status of the patient?

Dr. Field: Electrocardiography, X-ray, and so forth, are the standard methods, but probably more important is the actual functional capacity of the patient in regard to angina, congestive heart failure, hypertension, and so forth. We all are appreciative of the patient population who will have unpredictable myocardial infarctions and demise. We have run into the situation of patients being evaluated who seemed robust, healthy, and without symptoms of cardiac disturbance, who have a sudden fatal coronary before they ever come to a final decision as to hypophysectomy, so it is not necessarily related to intervention.

When we retrospectively divided the stalk section group into those who were under 40 at the time of the procedure versus those over 40, there was a striking difference in the end results, with 80 percent appearing to profit in the under 40 group and only 46 percent appearing to profit in the over 40 group. Perhaps the factor involved here is the amount of arteriosclerosis, that is of the nonspecific microvascular angiopathy. This, perhaps, is also borne out by our analysis of renal biopsies. The patients who have specific microvascular lesions referable to diabetes are the ones that seem to respond predictably. The amount of underlying nonspecific arteriolosclerosis might be considered a negative feature in an evaluation.

Dr. Fraser: I wondered if I might dare make a little comment on what might be described as Dr. Sweet's optimistic opening remarks (ch. 34). It was very difficult to end up with a conclusion that anything short of a surgical knife could be useful in destroying the pituitary. I wonder if we shouldn't also bear in mind, in weighing up the relative merits of different procedures, that there are at least three important considerations which have all got to be weighed qualitatively against each other. There is the effectiveness in removing pituitary function. There is the mortality (which is very different from morbidity). And there is the morbidity. All three have to be qualitatively judged. I think I might dare to say that Dr. Sweet rather emphasized the importance

of morbidity as if it was the same thing as mortality. Probably far more important than the nature of the operation is who does the operation. It is, I think, open to doubt if it is really very important to remove the whole of the pituitary.

Furthermore, with these nonsurgical radiations, we are really more demanding of knowing that the pituitary function has been obliterated. I have a feeling that these newer procedures have not yet provided evidence that they can ablate the pituitary effectively and consistently. I am afraid the number of tests that have been produced as evidence of this has, to many of us physicians, been inadequate. I am not sure it has yet been proved in these newer procedures of radiation, extreme heat, and extreme cold. I wondered if we should not leave more open what is the optimal procedure, concentrating more, perhaps, on the importance of the degree of ablation and the person who does it.

Dr. Schimek: Concerning the question as to whether pituitary ablation had any favorable effect on the nephropathy, when I was associated with the group at the Ford hospital that started in 1953 and 1954 to do pituitary ablation procedures, I recall that patients were selected both by being on the ophthalmic brink of disaster and also by being on the nephropathy brink of disaster. They had their kidney function followed quite carefully at that time, and the impression was unanimous that these nephropathies on the brink of disaster continued very rapidly into disaster.

Dr. Ray: In the face of progressive renal disease or advanced renal disease, we ought to be very circumspect about superimposing hypopituitarism on that patient, even though we can show it may benefit the retina for a period of the patient's remaining life. His renal disease is almost certainly going to go on as the formidable aspect of that case. In some of the discussion about whether renal disease was made worse by removing the pituitary, however, we seem not to give any consideration to the fact that any kind of operation (not just hypophysectomy), in which the patient is given a general anesthetic and has any kind of tissue trauma, will temporarily affect the renal function. BUN readily goes up, and it may take a while for it to come down. We have seen about the same effect, it seems to me, in patients who were subjected to hypophysectomy who had had borderline renal function.

Dr. Rand: In our group at UCLA we employ a psychiatrist as a silent partner. We do not identify the psychiatrist in the clinic, so the patient doesn't know initially that he is talking to a psychiatrist.

As far as the neurosurgical criteria for stereotaxic cryohypophysectomy, it is important to be sure that the sphenoidal sinus does not have an infection and that there is no significant previous history of infection. In order to reduce and eliminate the morbidity of nerve palsies, we keep the patient in a state of amnesia without pain by using appro-

priate intravenous medications. At the same time, in order to avoid aspiration of any stomach contents or blood from the nasal cavity, we intubate them. I know Dr. Field objects a bit, because he would like to see the patient asleep. On the other hand, when you quiz these patients after surgery, they remember very little, if any, of the operation. Yet, they can cooperate in detail, and we don't have any instances of extraocular or optic nerve palsies in a total of 100 patients who underwent this technique and in the 31 who underwent it specifically for diabetic retinopathy.

We initially began this procedure because we felt is was possible to produce either a partial or total hypophysectomy by a cryosurgical technique with a probe in the center of the gland. If it freezes, for example, to minus 120° at the tip of the probe, you can produce 75 percent destruction of the gland. On the other hand if you make multiple lesions, as you would for a thermal destruction, you can produce total or nearly total hypophysectomy, as we have learned in patients who died from cancer of the breast. In order to produce total destruction, it is advisable during the procedure to compress the carotid artery for 2 or 3 minutes. It is also possible to do a reoperation if you are not satisfied with the degree of hypophysectomy. Once again, relatively minimal surgical trauma is produced in these rather ill and brittle individuals.

Dr. Ray has rightly been concerned about puncturing the carotid artery in a stereotaxic operation. He and his group have written a very excellent article in the Journal of Neurosurgery (R. M. Bergland and others, J. Neurosurgery 28: 93–99, February 1968) showing the anatomical variations of the pituitary and its surrounding environment. We now routinely do angiograms to demonstrate the specific location of the carotid arteries, and thus avoid striking one with the drill. You can also outline the pituitary by retrofilling of the cavernous sinus.

We have only operated upon 31 of some 200 patients who were evaluated. The reason for this is not that I am not anxious to do operations, but that the ophthalmologists first select the patients. Drs. Roth and Straatsma and their group are very cautious about sending patients for operations. So are the internists. I think this accounts for our small number of patients.

Dr. Ray: I want to put a question to Dr. Rand and possibly to Dr. Zervas. Dr. Zervas' paper states that he feels that radiant heat really boils or burns the pituitary, and that the spinal fluid in the cisternal area affords very ample protection against the more important structures outside the sella. He wonders, however, whether the same obtains for cold. Is there a difference in protection by fluid against heat or cold?

Dr. Rand: We have done studies by passing thermocouples just distal to the tip of the probe, and, although the probe temperature may be reading minus 184° C., it may be only minus 10° C. 6 millimeters from the tip of the probe. We have one thing going for us in the pituitary. We do have the anastomosis of the superior and inferior hypophyseal arteries within the sella, and, if one doesn't project too far back in the sella, the incidence of diabetes insipidus is quite low. We have one patient, however, who continued to need treatement in this regard.

Dr. Zervas: I would hesitate to try to establish the differential effectiveness or desirability between the procedure we do and Dr. Rand's, because that would defeat the purpose we both set out to accomplish 7 or 8 years ago. Namely, we were very impressed with the approach, but not with the applicatory agent. The only point in our statement about spinal fluid circulation above the gland was that I wondered if a cold lesion which freezes the cerebrospinal fluid would be projected as ice toward the optic chiasm. I wondered, when you reached the point where an oculomotor palsy or visual disturbance occurred and were then forced to stop the lesion at this point, if you were certain at this point that you would achieve destruction of the marginal pituitary tissue.

Dr. Rand: We are not concerned about the appearance of extraocular nerve palsy. This may occur in 10 percent or so of patients. If you are watchful in observing these people, you will effect a reversal simply by shutting down the machinery, because you have not frozen the tissue. You have simply cooled it below 15° C. If you had frozen it, you would have had, at least for a time, a more permanent effect.

Dr. Ray: Allusion has been made several times to preserving the posterior lobe. Dr. Hardy will no doubt want to comment on his efforts in that direction. I think we ought to be quite clear about what this is meant to accomplish. If it is meant to prevent or minimize diabetes insipidus, we can talk to that point. But the fact remains that the anterior lobe, while it sometimes fairly easily separates through a clear line of demarcation, sometimes is wrapped around the posterior lobe from each side, either over it, or under it, or all of those. One thus runs a risk of leaving anterior pituitary tissue, and, in the presence of an intact stalk and portal system, this is not a very desirable feature of an attempt at total hypophysectomy.

Those of us who do the operation intracranially and see the structures from above are often enough impressed with the conical shape of the stalk as it rises through the opening in the diaphragm. This represents the existence of anterior pituitary cells running up along

the stalk, occasionally in a sizeable fashion. In those instances we would, of course, section the stalk above where it seemed to bulge from this conical extension of the anterior lobe. Ordinarily, I would certainly favor as little manipulation of the stalk as possible, by low section without clipping and without coagulation. Dr. Sweet, however, takes another attitude about this. He clips it high, and perhaps he has a point, but we felt that the less done in the way of manipulation in that region the less risk of interfering with small nutrient vessels to the visual apparatus and the less likelihood of degeneration in the nuclei in the hypothalmus and so on. The stalk, when it is cut, will bleed a little, but, if one is patient—and the operation does call for patience—it always stops. As a matter of fact, when the stalk is cut, there is much more likely to be nuisance bleeding coming from the pituitary side than from the hypothalamic side, owing to the fact that there is an ample blood supply to the pituitary having nothing to do with the stalk and portal system.

Dr. Hardy: I would like to add a few remarks concerning the surgical anatomy of the pituitary fossa and its contents, mainly the pituitary gland. The magnificient study by Ray and his coworkers (R. M. Bergland and others, J. Neurosurg. 28: 93–99, February 1968) is a serious warning about the anatomic variations of the size, contour, and shape of the hypophysis and of the anomalies of the surrounding structures which are likely to be present in any single case (even though they might be statistically encountered infrequently). When the hypophyseal fossa is directly exposed through an open procedure, either transcranial or transsphenoidal, and, moreover, when it is observed magnified with the surgical microscope, these anomalies are easily recognizable. Precaution is taken to avoid manipulations or damage to the structures.

For instance, the absence of the "concha type" of sphenoid sinus was encountered in five instances. We have devised a technique to reach the sella by chiseling off a tunnel with a diamond air drill. A midline expansion of the cavernous sinus was seen protruding in the sellar window on three occasions. Precaution was taken to open the dura in an avascular area. A carotid artery was seen protruding in the sella in four instances. In one of these, both carotids were seen almost kissing in the midline, and were surrounded by a kidney-shaped pituitary. The hypophysis could be removed in all these cases without complication. The most frequent anatomical variation was the presence of an arachnoidal cistern within the sella above the gland and extending sometimes in front of the pituitary. Under direct exposure, tearing of the arachnoid is easily prevented by covering it with a cotton pledget prior to the initiation of the pituitary dissection. However, if the arachnoid is occasionally torn off, producing cerebrospinal fluid leak

in the sella, adequate sealing is easily accomplished with a piece of fascia lata applied underneath the diaphragma sellae and maintained tightly in place with a piece of muscle packing the sella cavity. Afterwards, the sellar window is obliterated with a cartilagenous graft, taken from the previously removed nasal septum. Careful adherence to technique has overcome the possible complication of rhinorrhea.

In view of the extreme variability in the morphology of the pituitary body, one may be concerned about the hazards and complications attending the various indirect procedures with blind introduction of a probe to produce pituitary destruction in situ by heat, cold, ultrasound, or radioactive material. With these latter methods it would be wise, at least, to perform routinely preoperative angiographic studies together with the elegant technique of cavernous sinusography developed by Dr. Rand.

I agree entirely with the authoritative opinion of Dr. Ray: "The advantages of adequate surgical exposure are nowhere more obvious than in surgery of the pituitary." Indeed, the open transsphenoidal procedure with direct visualization under the microscope facilitates the recognition and management of the anatomic variations and anomalies about the sella, and permits a more certain removal of the anterior lobe or of the total pituitary gland. A complete removal can be ascertained only when the gland has been enucleated en bloc with its capsule.

Sometimes the posterior lobe is firmly attached in the shallow depression on the posterior wall of the sella, and there is no point in removing it, because this would induce unnecessary bleeding.

Dr. Ray: Do you put your patients to sleep?

Dr. Hardy: Yes. Always.

Dr. Balodimos: I am neither hot nor cold for any of the surgical procedures, but I wanted to point out that, in our experience and in the majority of the reports here, complete ablation has been found to correlate better with successful arrest of retinopathy. Consequently, I think that would be my aim in the treatment. I would think that persons who have rapid progression of retinopathy would be unfit candidates for proton beam radiation. They would be the ones who need a rapid method of therapy. In our experience proton beam has not worked until six and, in many cases, 24 months after the procedure. In addition, surgically unfit patients would have relatively low life expectancy if they have other problems from the kidney or heart which made them unfit for hypophysectomy, so I would vote for surgery in any suitable case.

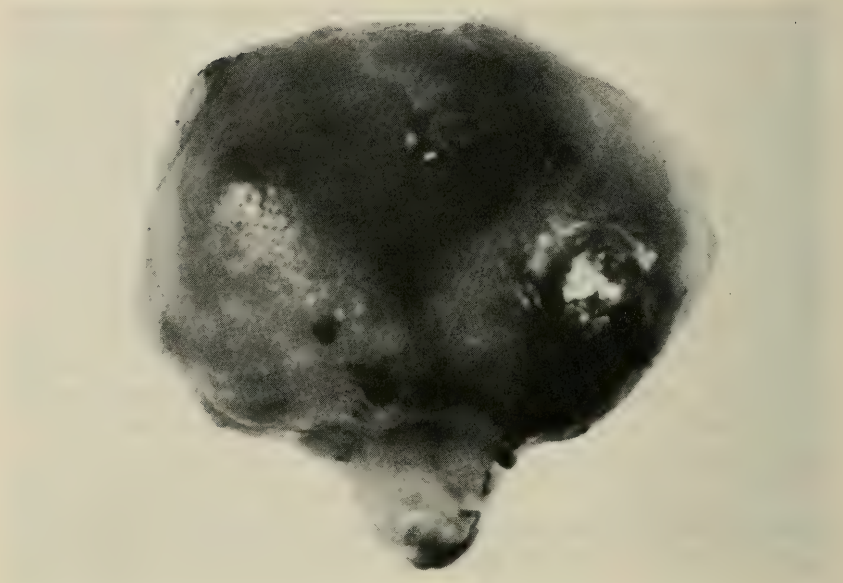

FIGURE 1.—*Specimen of a complete extracapsular enucleation of the pituitary after low stalk section. (Dr. J. Hardy)*

Dr. Kjellberg: With respect to the immediate past remark, what is the statistical difference in your two groups of hypophysectomy: intermediate versus so-called complete hypophysectomy? As I looked at those figures, I thought they were similar.

Dr. Bradley: The only difference in the two groups was that in the moderately ablated group, there were one or two out of three thyroid function tests which were still within the range of normal. They might be somewhat depressed, but were still within the range of normal. For hypophysectomy to be called maximal, all tests had to be compatible with pituitary hypofunction. There is no other difference between those two groups.

Dr. Kjellberg: Do you think that weakens your argument for the necessity of complete hypophysectomy or not, Dr. Bradley?

Dr. Bradley: I don't think our data would prove the point. We have too few patients in the slight hypophysectomy group to make a statement. Just because the percentages happened to show fewer who did well, the numbers are altogether too small for us to make this statement.

Dr. Fager: This is a good time, however, to raise the question of why we went from pituitary stalk section to partial extraction and then to total removal. It is not obvious from looking at the cases as

Dr. Bradley reported them, but when you get one or two patients who have a dramatic reversal of retinopathy following stalk section and then a recurrence of severe retinopathy coincident with return of pituitary function, this changes your attitude a little.

This matter of the circulation in the gland has been studied very extensively, and it is still a big question in my mind. I am afraid I will probably take issue with Dr. Sweet on the question of regeneration of the stalk or vessels. My own personal feeling (and I may not be right) is that this is of no significance whatever. What led me to change procedures is the only operative mortality in our group. This lady died 3 weeks after surgery, and the surgery was a pituitary stalk section which was very complete. This gland was removed at autopsy, and the zone of necrosis in the anterior lobe was quite definite, but a good bit of the anterior lobe remained viable. The big question is, What happened with blood flow? She had a sizable vein in the periphery of this viable tissue providing communication with the outside world. Perhaps the blood supply is going up through the venous sinusoids rather than coming down through the hypophyseal system. Thus, you have a gland in an inconsistent state of infarction that can resume its function months and perhaps years later.

Dr. Zervas: There are a few points I wanted to make in defense of the stereotaxic method. In only one case out of 97 did we find the carotid artery medial to the extremity of the hypophysis. In 145 cases of hypophysectomy, we have yet to encounter a return of arterial blood after either midline or lateral puncture. We attempt to be within 4 millimeters of the midline with any lateral electrode. In the last four cases we kept in the midline. We attempt to demonstrate the diaphragma sellae and any variations in position of the anterior lobe of the pituitary. Because of variations in position, we feel that all punctures must be low.

In our attempts to spare the posterior lobe, particularly the bottom portion of the stalk, we showed that the longer the sella turcica, the farther is the anterior edge of the pituitary stalk. We have attempted to be very careful in heating up tissue on the very surface of the gland.

To overcome the problems that a surgeon faces when he has a blind procedure (such as the stereotaxic method), we designed our probe to give us a tactile sensation of the contents of the pituitary fossa. One can thus feel, as the tip of the electrode hits bone, diaphragma sellae, artery, capsule of the pituitary, or the extremity of the gland, and one knows where to make lesions and how far laterally these must be made. Because of this, we have been able to bring about effective hypophysectomy.

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Finally, the most important problem anybody using the transsphenoidal method has faced is that of cerebrospinal fluid. This was the objection to that procedure devised by Dr. Rand. This is why we went our separate ways. Since we have used our silicone plug, we have had one leak in the fourth patient, and none since, in a total of 65. In our first 26 patients, using a bilateral technique, we had only one leak. This occurred in a patient in whom the punctures had been placed too high. This procedures was somewhat similar to that of Dr. Rand's, where he also encountered CSF very rarely. Then we changed to a midline technique. We had seven cases of rhinorrhea. All the anatomical studies now show that there is an arachnoidal diverticulum in the midline in a significant number of patients. Dr. Ray showed this in his own work. When we changed over to either a muscle or silicone plug, this particular complication was avoided.

Dr. Ray: I wanted to tell you, Dr. Zervas, that I thought of you this past week when we had two consecutive patients without any diaphragma sellae, and I admired your ability to probe the thin capsule of the pituitary gland and not transgress it.

I daresay all the ablators here will go home and continue to use their own methods. Perhaps the most useful statement here has been that of Dr. Fraser's, in which he pointed out that in each man's hands, he performs his own method best.

PART V

Photocoagulation

CHAPTER 35

Ruby Laser Photocoagulation in Treatment of Diabetic Proliferating Retinopathy: Preliminary Report

LLOYD M. AIELLO, M.D.
WILLIAM P. BEETHAM, M.D.
MARIOS C. BALODIMOS, M.D.
BERNARD I. CHAZAN, M.R.C.P.
ROBERT F. BRADLEY, M.D.

GENESIS

This paper pertains to the retinopathy which occurs in a small percentage of patients with diabetes mellitus; when it appears, it is usually progressive and often leads to severe visual impairment if not blindness.

The ophthalmoscopic appearance is well known to all participants of this symposium and needs no description, but, for the purpose of orientation, some or most of the following items are observed: distention of the retinal veins, venous varicosities, patches of neovascularization (frequently on or from the optic disc but found also in various portions of the retina), preretinal and/or vitreous hemorrhages, fibrous tissue bands and sheets often from the disc area and often extending as festoons along the major vessels, and sometimes secondary retinal separation.

The rate of progress of this type of retinopathy varies markedly but in a large group studied by me [1] an average deterioration seemed to be about one degree (slight, moderate, marked, severe) per 1.5 to 1.9 years or, in other words, 6 to 8 years from onset to a severe degree of retinopathy (which would probably be associated with less than legal blindness). In a similar group of more than 1,100 patients, 350 were well followed by numerous office visits over a period of many years; 35 of these 350 patients progressed to a certain stage, a few

[1] W. P. Beetham, M.D.

From the Diabetes Foundation, Inc., the Joslin Clinic, the New England Deaconess Hospital, and the Elliott P. Joslin Research Laboratory, Boston, Mass.

This study was supported by grants from the John A. Hartford Foundation, the Joseph M. and Evelyn R. Weidberg Foundation, the Adler Foundation, Inc., the Massachusetts State Grange, and the U.S. Public Health Service (AM–04146). Dr. Chazen had a "Fight for Sight" Postdoctoral Research Fellowship (F–206) of the National Council to Combat Blindness, Inc.

with good vision, most with markedly impaired vision, and some with less than legal blindness (*1*). However, then the destructive process seemed to stop and become quiescent and remain more or less arrested. The fundus picture in this arrested group showed much less venous distention; the arterial tree became smaller and somewhat attenuated; the patches of neovascularization seemed to shrink and some to disappear; the fibrous tissue became thin, lacelike and reticulated; often the optic disc showed some pallor suggesting mild atrophy; and above all, the hemorrhages and microaneurysms became scarce or absent. Definitely, the venous-arterial vascular balance in the retina and choroid had been changed and much less vascular activity existed.

When a good opthalmoscopic result is obtained by pituitary gland destruction, a similar fundus picture is described. We have definite evidence that less retinal vascular activity occurs in most of the successful results from pituitary ablation. The massive destruction of choroid and retina that is sometimes seen in nonspecific disseminated chorioretinitis often causes little or no visual disturbance, yet the retinal arteries and veins appear small in caliber and the optic nerve may show some mild evidence of pallor or atrophy. A few reported cases of unilateral optic atrophy and also unilateral chorioretinitis in diabetic patients with retinopathy have been observed to have more retinopathy and more vascular disease in the eye without the optic atrophy or chorioretinitis than in the affected eye, in which the vascular tree is already narrowed and contracted.

For many years photocoagulation of portions of the retina and choroid with the xenon light (a white light with multiple wavelengths) has been successfully used. Often, however, photocoagulation with this light in patients with severe diabetic retinopathy has been done too late as a last resort and with little chance of help or improvement expected. The extensive use of the xenon photocoagulation (*2*, *3*, *4*, *5*, *6*) has successfully destroyed patches of neovascularization and fragile retinal vessels; but when this light is used extensively and in a diffuse manner, large defects in the visual field may result, active hemorrhage can occur, and the possibility of increasing the fibrous tissue component is great, with resulting traction bands and later retinal separation.

With these observations and information as a background, we have attempted to reduce the vascular activity in the posterior portion of the globe by creating numerous small, relatively harmless scars in the retina and choroid with the use of the ruby laser beam. The beam, the procedure used, the criteria used for the selection of patients, and the available results to date are herewith reported, and must be interpreted as a "preliminary report." The project has been pursued

diligently for some 15 months. However, a 5- or 6-year study is planned since we believe the long-time outcome and results are more important than the short-time impressions.

INTRODUCTION

In order to test the hypothesis of reducing vascular activity of the retina and choroid for its possible beneficial effects on the course of diabetic proliferating retinopathy as outlined by Dr. Beetham, the ruby laser photocoagulator was considered the most promising coagulator available. Multiple small, deep, chorioretinal lesions can be properly spaced over the entire posterior pole without producing sector field defects. The maculopapular bundle, disc, and macular areas were avoided (fig. 1).

Since February 1967, 214 patients have been or are under treatment for neovascular proliferating diabetic retinopathy using this technique. As of January 1, 1968, 102 patients had completed treatment and of these, 91 represent the 6- to 8-month followup group presented in this preliminary report. Eleven patients were not included because of inadequate followup data. Only one eye of any patient has been

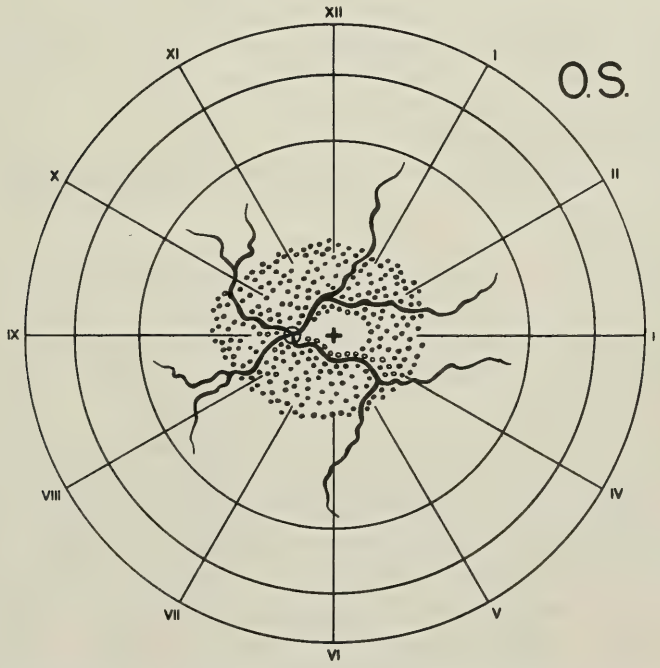


FIGURE 1.—*Diagrammatic illustration of the diffuse placement of 2.5° ruby laser burns in the treatment of diabetic proliferating retinopathy.*

treated by laser photocoagulation, the other serving as a control. In four of the 91 cases, the untreated eye progressed extremely rapidly with the onset of new vessel formation on the disc. Since three of the four treated eyes were showing remarkable improvement and the other one hemorrhaged in the post-treatment phase, the second eye was treated.

It was our general impression, substantiated later by fluorescein studies and clinical results, that several characteristics of the angiopathy influenced the progress and prognosis: (1) neovascularization at retinal level versus elevated; (2) disc neovascularization in three categories: very early changes at the disc, new vessels along the retina from the disc, or elevated fans from the disc; (3) the presence of arteriosclerotic retinal disease along with neovascularization; and (4) the presence or absence of fibrous proliferation. Therefore, the following group classification is employed in general order of worsening prognosis in terms of response to laser photocoagulation therapy.

I. Advanced angiopathy without definite neovascularization (i.e., microaneurysms, red dot and blotch hemorrhages, and venous distention). Only one or two cases fall into this group and there is insufficient followup to report results.
II. Neovascularization of retina at retinal level except disc.
III. Very early neovascularization of disc with or without other neovascularization (usually flat in/on retina).
IV. Neovascularization of retina in presence of much arteriosclerotic retinal disease.
V. Neovascularization and fibrous proliferation (elevated).
VI. Advanced neovascularization of disc—flat along the retina, with much "diffuse" angiopathy.
VII. Advanced neovascularization of disc—elevated rete into vitreous.
VIII. Advanced neovascularization elevated from retina into vitreous with or without elevated disc vessels. Not acceptable for laser photocoaulagtion.

The untreated eye does not necessarily fall into the same group classification or severity of disease as the corresponding treated eye. Such a control study in which both eyes are almost equal in degree of neovascular change will have to await further long-term study and accumulation of greater numbers. It must be stressed that this report provides only short-term impressions. Only time will provide significant data. However, since this study provides a unique and relatively pure approach to the stated hypothesis, we feel it important to present this preliminary report.

EQUIPMENT

(1) American Optical pulsed ruby laser photocoagulator (6943A°) was chosen primarily because of the superior indirect method of observation with the erect image and the large field of view. Other characteristics of this laser are the high transmission of the radiant energy by the ocular media, high absorption by the retina and choroid, primarily the pigment epithelium, monochromic energy emission, and short duration of laser emission (*7*).

(2) Both the indirect and the direct ophthalmoscopes were used for preoperative studies and retinal drawings.

(3) The Goldmann three-mirror lens and the Zeiss motorized slit lamp are presently being employed for vitreous studies. Results of these observations are not included in this report.

(4) The Zeiss fundus camera was used for color and fluorescein fundus photography. Color photographs were taken of nine areas in each fundus in an effort to assist documentation of the general diabetic pathology.

(5) Fluorescein photographs of the retina were taken in most patients before the application of the laser photocoagulation and are planned at 6- to 12-month intervals thereafter. Ten milliliters of a 5 percent sodium fluorescein solution was injected by a Cordis injector via a small catheter inserted in the antecubital vein. Serial photographs were taken ½ to 2 seconds apart usually for the first 30 seconds. We concentrated usually on the disc and the macular area or sometimes in other areas of the retina presenting special interest. Thirty to 60 minutes later, a second injection was given for the other eye followed in some cases by a third injection for visualization of a special area of either fundus.

CLINICAL MATERIAL AND METHODS

Initially, all patients were referred to the ophthalmologists [1] by other physicians, primarily from the Joslin Clinic. The examination included full ocular evaluation: refraction, biomicroscopy (especially for iris vessels and lens changes), pupillary size and reaction, field examination, tonometry, and ophthalmoscopic description through the dilated pupil. The latter was dictated with particular emphasis on the vitreous and retina as follows: (*a*) The degree of non-neovascular angiopathy (i.e., red dots, blotches, pre-retinal and vitreous hemorrhages), (*b*) areas of new vessel formation with their exact location

[1] Aiello, L. M., and Beetham, W. P.

and with comment as to whether they were thought to be elevated or not, (*c*) degree and location of fibrous proliferation, (*d*) the character of the major vessels with regard to irregularity, tortuosity, varicosity, dilatation and kinking, and (*e*) the extent and location of cotton-wool and waxy exudates. At this office examination, the patient was either accepted or refused for laser photocoagulation therapy. Those patients too far advanced in the angiopathic phase or progressing too rapidly to overcome the effects with present photocoagulation techniques were recommended for pituitary ablation if they otherwise met the ophthalmic and medical criteria (*8*). The presence of extensive fibrous proliferation and/or secondary retinal detachment generally precluded any form of therapy.

Two days prior to the initial treatment, the patient was admitted to the Hospital Teaching Clinic, an ambulatory unit of the New England Deaconess Hospital, Boston, for further ophthalmic and medical evaluation. Color fundus photography and fluorescein studies of each fundus were performed on each eye as described above. Retinal drawings with the indirect ophthalmoscope were prepared and correlated with the direct ophthalmoscope findings at the initial office visit. More recently vitreous examination with the three-mirror lens and slit lamp has been performed. Orientation of the patient during the preoperative evaluation period was very important. The following points were stressed: (1) More than one treatment session would be necessary, and on an average, two or three. (2) Close followup would be required at 4- to 6-week intervals during the first 5 or 6 months. (3) The patient should avoid severe insulin reactions which, in our experience, place stress on the abnormal vessels and tend to provoke vitreous hemorrhage and failure in treated and untreated eyes. (4) The treatment would have no beneficial or adverse effect on macular function. (5) Only one eye would be treated by this method except in rare circumstances such as: (*a*) marked progression of untreated eye with marked improvement of treated eye, and (*b*) marked progression of untreated eye with loss of treated eye of a patient who is not a candidate for pituitary ablation. (6) The purpose of the treatment is an attempt to decrease the chance of future hemorrhage, not a guarantee of such benefit. The treatment would not cure the basic disease but perhaps would alter its course. Prognosis with or without treatment was discussed.

The general technique for laser photocoagulation was carried out as described by Zweng and Flocks (*9*), Campbell, et al., (*10*), and L'Esperance (*11*, *12*). No premedication was used. The pupils were dilated with Mydriacyl 1 percent and Neosynephrine 10 percent. No local anesthesia was used. The patient fixated on the ceiling or on his

thumb. The instrument setting was aperture 2.5 (burn size, 0.75 millimeter) and the power setting was calibrated for the individual patient in an attempt to produce grade II lesions (*10*). In general, the greater the degree of pigmentation of the fundus, the lower the power setting. At each treatment, approximately 200 to 300 applications of grade I, II, and/or III lesions were applied in all areas of the posterior pole sparing the disk, macula, and maculopapular bundle (fig. 1). As far as possible, there is usually a small interval of normal retina between each lesion except perhaps in areas of new vessel clumps where the burns may have been placed contiguously. The number of lesions per treatment was usually limited by the corneal drying and clouding, the cooperation of the patient, and the inadvisability of treating over recently formed lesions (fig. 2).

The patients were discharged on the following day with instructions to avoid heavy lifting, severe emotional stress, and severe insulin reactions. Followup treatment sessions were conducted on an outpatient basis at 4- to 6-week intervals. The total number of applications, in the range of 600 to 800, required two to four treatment sessions, depending on the degree of retinopathy and the response to treatment.

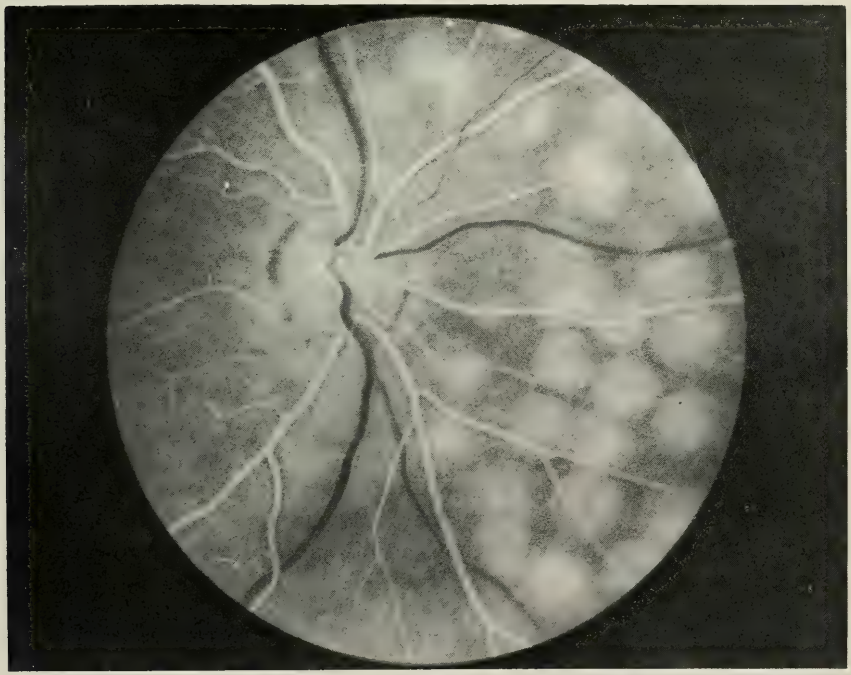


FIGURE 2.—*Fluorescein angiography 3 hours following application of laser lesions. The dye appears early in the area of the discrete yellow-white lesions and is retained here after disappearance of dye from the surrounding retina.*

Followup examinations included direct and indirect ophthalmoscopy, field examination, complete ocular examination, repeat fundus photographs at frequent intervals, and repeat fluorescein studies.

Statistical evaluation of the observed differences was made by using the Chi Square Test.

Evaluation of the results included study of the effect on (1) characteristics of the major vessels, (2) new vessels, (3) untreated areas of retina, (4) vitreous contraction, (5) fibrous proliferation, (6) in two cases, subsequent retinal detachment. The O'Hare Classification [1] was adhered to with the following modifications: H_1, included preretinal hemorrhage as well as minimal vitreous hemorrhage; Nx, no new vessels seen after treatment, although present before treatment; and Fx, fibrous tissue at retinal level before or after treatment (often reticulated after treatment of a neovascular patch). To date, 23 patients have had followup fluorescein studies to add further to the understanding of the clinical improvement or failure. Sector field defects and scotomata corresponding to the small lesions were not found on routine tangent screen and/or perimeter examination as a result of photocoagulation therapy. More sensitive field techniques were not employed. The results of treatment were evaluated according to the group classification I through VIII described above. Groups I and VIII are not represented in this report. The clinical groups will be referred to as II through VII in the tables. The totals for a given group of patients in one table will not necessarily correspond to the totals in another table because of (1) the treatment of the second eye in four cases, (2) the availability of specialized data as fluorescein studies, or (3) the presence of vitreous hemorrhage in the untreated eye initially precluding classification of the neovascular state.

As mentioned before, the untreated eyes are not necessarily of the same group classification as the treated eyes. Tables four to nine summarize the results of treatment using three parameters: (*a*) O'Hare Classification, (*b*) fluorescein angiography, (*c*) and general clinical impression which embodies (*a*) and (*b*) in addition to other factors such as untreated areas of retina, large vessel pattern, and vitreous changes.

Tables 7 and 8 summarize the fluorescein angiographic studies. "DA" refers to the extent of "diffuse angiopathy" graded 1 to 4 in increasing severity. The following characteristic fluorescein changes are embodied in the term "diffuse angiopathy": (*a*) distended, tortuous, and irregular veins and venules, (*b*) multiple capillaries visible with fluorescein which are not usually seen, (*c*) many sacculations (microaneurysms) attached to the vessels, (*d*) areas of capillary clo-

[1] O'Hare Classification, p. xxi.

sure, and (*e*) prolonged retention of dye in the walls of arterioles and venules and in other abnormal areas (figs. 3, 7). Judgment of this classification is based on the degree of the above pathology present on the basic fluorescein view of the disc and macular area of posterior pole. The activity of the fibrous tissue is judged by the presence or absence of retained dye. The "disc vessel leak" category refers to the characteristic presentation of dye in the disc vessels with rapid and early leakage of dye into vitreous or preretinal space (fig. 9). The "noncharacteristic disc vessel pattern" is exemplified by the description of a patient by Dollery and Oakley (*13*) in which there is a markedly abnormal "probable" new vessel pattern without characteristic leakage but with much superimposed diffuse angiopathy (figs. 7, 8).

The visual acuity and visual indices were not correlated in this report. In all instances, the vision remained stationary unless vitreous hemorrhage or macular damage secondary to exudate or pigmentary degeneration ensued.

General medical evaluation of all the patients was undertaken during the initial admission to the hospital teaching clinic and during subsequent visits. The clinical information is presented in tables 1, 2, and 3. For purposes of analysis, groups IV, V, VI, and VII are considered together. The terms are defined as follows: (1) Split insulin dose indicating brittle diabetes; (2) proteinuria with values of greater than 50 milligrams per 100 milliliters; (3) elevated BUN with persistent readings above 25 milligrams per 100 milliliters; (4) hypertension if diastolic exceeded 90 millimeters Hg.; (5) postural hypotension with a fall in systolic or diastolic pressure of 25 millimeters and 20 millimeters Hg. respectively; (6) CVA referring to cerebrovascular accident; (7) peripheral vascular disease as measured by absent pedal pulses or by presence of necrotic lesions; (8) EKG abnormalities as indicated by pathological Q wave or ST–T changes; and (9) persistent hypercholesterolemia of greater than 260 milligrams per 100 milliliters.

There were no significant differences in the clinical data between ophthalmic groups II and III. However, in comparison to groups II

TABLE 1.—*Group treated*

Clinical group	Total patients	Sex		Present Age	Age range	Average age onset DM	Average duration
		Male	Female				
II	32	17	15	38.3	26–62	16.0	22.3
III	38	17	21	38.6	24–71	15.7	22.9
IV	5	5	0	42.4	33–55	11.0	31.4
V	4	2	2	38.2	29–47	13.2	25.0
VI	6	0	6	24.4	21–29	8.0	16.3
VII	6	6	0	43.8	24–62	25.1	18.7

TABLE 2.—*Correlation of medical data*

Clinical group	Total patients	Acidosis history	Split insulin therapy	Peripheral edema	Diuretic therapy	Proteinuria	High BUN	Hypertension	Postural hypotension	Hypercholesterolemia	Periph. Vasc. Disease	Abnormal EKG	CVA
II	32	5	8	2	6	15	6	15	8	4	8	7	1
III	38	4	15	10	10	17	4	11	6	1	5	12	0
IV, V, VI, VII	21	5	13	10	10	10	7	10	5	11	7	5	1
Total	91	14	36	22	26	42	17	36	19	16	20	24	2
Percent of total		15	40	24	29	46	19	40	21	25	22	26	

TABLE 3.—*Diabetes type and complications in clinical groups of retinopathy.*

	Stable diabetes				Unstable diabetes				Grand total
Clinical group	Diabetic complications	No complications	Total	Percent	Diabetic complications	No complications	Total	Percent	
II	15	6	[1] 21	66	9	2	[1] 11	34	32
III	13	6	19	50	15	4	19	50	38
IV–VII	7	0	[1] 7	33	12	2	[1] 14	67	21
Total	35	12	47	52	36	8	44	48	91

[1] Difference significant ($P < .05$).

and III, the more severe ocular groups (IV, V, VI, and VII) had a greater incidence of peripheral edema ($P < 0.01$), and hypercholesterolemia ($P < 0.05$) (table 2). There was a higher frequency of unstable diabetes (as evidenced by a history of acidosis and/or split insulin dose) with increasing severity of retinopathy (table 3). Greater numbers in groups IV, V, VI, and VII are required before they may be considered separately or before more detailed analysis would be fruitful.

RESULTS

Group II: Neovascularization primarily at the retinal level, excluding disc (fig. 5)

The neovascular pattern seems to have been favorably affected by laser photocoagulation (table 4). Fifteen of 33 eyes showed definite improvement to the lesser classification—while in 11 of 33 (or one-third) no neovascularization was visible ophthalmoscopically follow-

TABLE 4.—*Change in "N"* [1] *classification of treated and untreated eyes*

Clinical group	N_2—N_1	N_2—Nx^2	N_1—Nx	N_2—N_2	N_1—N_1	N_1—N_2	Total Nx^2
II							
Rx eye	15	7	4	6	1		33
No Rx eye	1			12	9	4	26
III							
Rx eye	15	7	4	7	3		36
No Rx eye	1			15	11	1	28
IV							
Rx eye	3		1		1		5
No Rx eye	1			1	1		3
V							
Rx eye	2	2					4
No Rx eye					2		2
VI							
Rx eye	3	1	1	1			6
No Rx eye				4	1	1	6
VII							
Rx eye	2			4		1	7
No Rx eye	1			4			5
Totals	Improved	Percent	Stable	Percent	Worse	Percent	Total
Rx eye	67	73.6	23	25.3	1	1.1	91
No Rx eye	4	5.7	60	85.7	6	8.6	70

[1] See O'Hare Classification, p. xxi.
[2] Nx=No new vessels seen after treatment although present before treatment.

ing treatment ($N_2 \rightarrow Nx$ or $N_1 \rightarrow Nx$). In other words, all but seven had definite improvement of the neovascular state. In comparison to the course of the untreated eyes, the beneficial effect of treatment has high statistical significance ($P < .001$).

Table 5 illustrates that over half of the patients experienced no hemorrhage either before or after treatment. The hemorrhage of four of the treated eyes cleared following photocoagulation, while an equal number experienced hemorrhage at some time following treatment. The untreated group had the same number of hemorrhages in post treatment phase, but in none was there clearing of preexisting hemorrhage.

Only three of 32 treated eyes in this group II exhibited fibrous proliferation other than a minimal fine net flat on the retina associated with the new vessel formation either before or after therapy (Fx) (table 6). Furthermore, none of the Fx patients progressed to F_1 or F_2. The two patients whose fibrous component progressed to F_2 experienced prior vitreous hemorrhage postoperatively.

It is interesting that most of the patients in this treated group have moderate-to-minimal diffuse angiopathy (DA 1 and 2) (table 7), yet may have had quite extensive neovascularization beyond the disc-macular view (28 of 33 fell into the N_2 classification) (fig. 4). Of equal or greater interest is the indication from the data that there is a tend-

TABLE 5.—*Change in "H" [1] classification of treated and untreated eyes*

Clinical group	H_1—H_0	H_0—H_0	H_1—H_2	H_2—H_2	H_0—H_1	H_0—H_2	Total
II							
Rx eye	4	18	5	1	4	1	33
No Rx eye		13	7	5	3	2	31
III							
Rx eye	3	22	4		4	1	34
No Rx eye	2	17	6	4	1		30
IV							
Rx eye		3	1		1		5
No Rx eye		1	2	1	1		5
V							
Rx eye	2		1		1		4
No Rx eye		2	1				3
VI							
Rx eye		5				1	6
No Rx eye		4			2		6
VII							
Rx eye	1	1	2			3	7
No Rx eye		2	3				5

[1] O'Hare Classification, p. xxi.

ency for overall improvement of the diffuse angiopathy in the untreated disc-macular area as well as in the treated area (table 8).

Group III: Early neovascularization of disc, usually with neovascularization elsewhere (fig. 6)

As in group II, the majority (26 of 36) of the treated eyes experienced a decrease in the amount of neovascularization (table 4). In fact, at the 6- to 9-month followup, in 11 of the 26 improved eyes, no new

TABLE 6.—*Change in "F" [1] classification of treated and untreated eyes*

Clinical group	F_0—F_0	Fx [2]—Fx	F_0—Fx	F_1—F_1	F_2—F_2	F_0—F_1	F_0—F_2	F_1—F_2	Total
II									
Rx eye	20	8	1	1			1	1	32
No Rx eye	12	2	1	4	4	1	1	1	26
III									
Rx eye	22	5	2	4		4			37
No Rx eye	22	2		1	7			2	34
IV									
Rx eye	4			1					5
No Rx eye	3			1					4
V									
Rx eye				2	2				4
No Rx eye	2				2				4
VI									
Rx eye	5								5
No Rx eye	4			2					6
VII									
Rx eye	3						1		4
No Rx eye	3			1	1				5

[1] O'Hare Classification, p. xxi.
[2] Fx-Fibrous tissue at the retinal level before or after treatment (often reticulated after treatment of a neovascular patch).

TABLE 7.—*Fluorescein evaluation before treatment*

Clinical group	DA 1	DA 2	DA 3	DA 4	H 2	Fibrous tissue		Leak disc vessels		Unusual disc vessel pattern	Disc vessels—No
						Active	Inactive	Yes	No		
II											
Rx eye	6	10	11								27
No Rx eye	2	8	9	1	6						20
III											
Rx eye	8	7	9	5				27	2		
No Rx eye	7	3	5	4		2	1	4			
IV											
Rx eye			3	2				5			
No Rx eye		1		1				2			
V											
Rx eye		1	2	1		4		4			
No Rx eye		2						1			
VI											
Rx eye			4	2						6	
No Rx eye			3	1		1				1	
VII											
Rx eye		2	2	2				6			
No Rx eye		1	2	1		1		2			

vessels at all were visible clinically. The majority of the untreated eyes remained unchanged in their neovascular classification (N_1 or N_2). The difference between the treated and untreated groups is statistically significant ($P < .001$).

About two-thirds of the treated eyes had no hemorrhage, preretinal or vitreous, before or after therapy (table 5). Three of seven eyes with hemorrhage (H_1) cleared following laser photocoagulation, while five eyes experienced hemorrhage during the 3-month treatment period or later on. Four of the five were H_1 and their overall neovascular component did not necessarily progress.

As in group II, the majority (27 of 37) had no fibrous proliferation or Fx (table 6). The treatment did not seem to affect the fibrous proliferative process already present and did not promote it unless vitreous hemorrhage became part of the picture.

The diffuse angiopathy was perhaps slightly more marked than in group II with a general shift toward DA 4 (table 7). Again, although the numbers are small, the treated eyes seemed to show a general improvement toward less angiopathy in the critical disc-macular zone (table 8). A most encouraging and hoped-for effect was an apparent change from leaking disc vessels to nonleaking ones, which in some cases were not even demonstrable as new capillaries on fluorescein

TABLE 8.—*Fluorescein studies in treated and untreated eyes*

Clinical group	DA 1	DA 2	DA 3	DA 4	H2	Fibrous tissue		Leak disc vessels		Unusual disc vessel pattern	Disc vessels—No
						Active	Inactive	Yes	No		
II											
Rx eye:											
Before	1	3	3								7
After	5	1	1								7
No Rx eye:											
Before		2	4								6
After	1	2	2	1							6
III											
Rx eye:											
Before	1	3	5	3				11	1		
After	5	3	3	1				4	1		7
No Rx eye:											
Before			2	2		1	1	4			
After			2	2		1	1	4			
IV											
Rx eye:											
Before				1				1			
After	1										1
No Rx eye:											
Before				1				1			
After			1					1			
V											
Rx eye:											
Before		1				1		1			
After					1						
No Rx eye:											
Before		1									1
After			1					1			
VI											
Rx eye:											
Before											
After											
No Rx eye:											
Before											
After											
VII											
Rx eye:											
Before		1	2	1				4			
After	2				2		2		2		
No Rx eye:											
Before		1		1				2			
After		1	1					2			

angiography. Followup studies on four untreated eyes showed no improvement of the disc vessel pattern.

Group IV: Neovascularization of retina in presence of arteriosclerotic retinal disease

The numbers are small in this group (table 1). However, our impression has been that, in the presence of rather severe sclerosis (characterized by white lines usually beyond the neovascular patches) the

neovascular patches have responded dramatically to a much reduced number of laser applications. This would suggest that the retina-choroid vascular pattern has not quite been compensated to permit neovascular arrest until a slightly greater number of nonfunctioning areas has been added (table 4).

Hemorrhage and fibrous proliferation were not major problems in these few cases (tables 5, 6). There was a marked reduction in DA and in one case a disappearance of the new vessels at the disc 6 months after treatment, as demonstrated on fluorescein angiography (table 8). New vessels elsewhere on the retina had also disappeared ophthalmoscopically, or if still present, did not fill with fluorescein.

Group V: Neovascularization and elevated fibrous proliferation

Laser treatment in the presence of fibrous proliferation apparently had a beneficial effect on the neovascular component, probably without provoking increased fibrosis (tables 4, 5, 6, 7, 8). However, when vitreous hemorrhage ensued in one case, secondary retinal detachment followed; the laser scars did not seem to play a preventive role. Certainly the numbers are too small to draw any statistical conclusions.

Group VI: Advanced neovascularization from disc along retina (figs. 7, 8)

The picture of many fine "new" vessels radiating from the disc in all directions along the retina provides a shocking appearance to the posterior pole (fig. 8). There may be many small nests of new vessels scattered over the entire posterior pole with many interspersed red dots (microaneursyms), blotches, and a markedly irregular venous pattern (fig. 7, 8). Surprisingly, five or six of the treated eyes responded to laser therapy with significant improvement—whereas in the untreated eyes (also classified in group VI, but less advanced compared to treated eyes in these cases), the angiopathy remained stable or became worse (table 4). The one treated case which hemorrhaged did so following a series of severe insulin reactions and unconsciousness (table 5). Otherwise, the hazard of spontaneous hemorrhage seems to be less than in groups III and VII. Fibrous proliferation is not a major part of the process in this group, at least prior to vitreous hemorrhage (table 6).

Angiography revealed severe diffuse angiopathy and the vascular pattern of irregular small vessels on the disc and extending in all directions along the retina but not necessarily connected to disc (figs. 7, 8). Many of the structures described as new vessels on clinical ob-

servation could not be so definitely defined on fluorescein angiography. Dollery and Oakley (*13*) have questioned whether these are "new capillaries" or "dilated capillaries." At present, followup fluorescein studies on this small group are not available (table 7).

Group VII: Advanced neovascularization of disc—elevated rete into the vitreous (fig. 9)

This group responded poorly to laser photocoagulation (tables 4, 5, 6, 7, 8). Although two of seven showed some improvement, the others remained stable or became worse in the neovascular category. Three had severe vitreous hemorrhages with loss of useful vision. Followup time is inadequate but one went on to severe fibrous proliferans as the hemorrhage cleared. The two eyes showing improvement in "N" classification also improved with regard to diffuse angiopathy and leakage of disc vessels (tables 4, 8).

General clinical impression, groups II–VII (table 9)

The general clinical impressions of the effect of laser therapy on diabetic neovascular proliferating retinopathy documented in table 7 were derived through direct and indirect ophthalmoscopic examinations and fluorescein studies with consideration of all of the param-

TABLE 9.—*General clinical impression of effect of ruby laser photocoagulation*

Clinical group	Worse	Stable unchanged	Improvement			Total
			Slight	Moderate	Marked	
II						
Rx eye	3	3	6	12	9	33
No Rx eye	11	21	1			33
III						
Rx eye	4	3	3	17	11	38
No Rx eye	19	14	1			34
IV						
Rx eye			1	2	1	4
No Rx eye		2	1			3
V						
Rx eye	1		1	2		4
No Rx eye	1	3				4
VI						
Rx eye	1		1	2	2	6
No Rx eye	3	3				6
VII						
Rx eye	4			2		6
No Rx eye	3	1	1			5
TOTALS						
Rx eye	13	6	12	37	23	91
Percent	14.3	6.6	13.2	40.7	25.2	
No Rx eye	37	44	4	0	0	85
Percent	43.5	51.8	4.7			

eters of neovascular angiopathy and its attendant complications. In order to remove subjective bias as much as possible, the statistical analyses grouped the total patients of all group classifications as follows: (*a*) In the treated group—worse, stable, and slight improvement versus moderate and marked improvement, and (*b*) in the untreated group—stable versus any improvement. In the treated eyes, as compared to the untreated, the regression of the neovascular retinopathy was definite and highly significant ($P < .001$). The favorable response to treatment in group II and group III (each considered separately) after 6- to 9-month followup was also statistically significant ($P < .001$). The small numbers of groups IV through VII precluded statistical analysis.

DISCUSSION

In order to test the hypothesis put forth in the introduction, a method of producing disseminated chorioretinal lesions similar to those of arrested diabetic proliferating retinopathy, old chorioretinitis, and retinitis pigmentosa, multiple xenon photocoagulation applications (*2*, *4*, *5*, *6*) had to be employed. However, this must be accomplished with minimal complications—above all without sector field

FIGURE 3.—*Diffuse angiopathy in the disc-macular area (DA 3). See text.*

FIGURE 4a.—*Minimal diffuse angiopathy (DA 1) was present in the disc-macular area.*

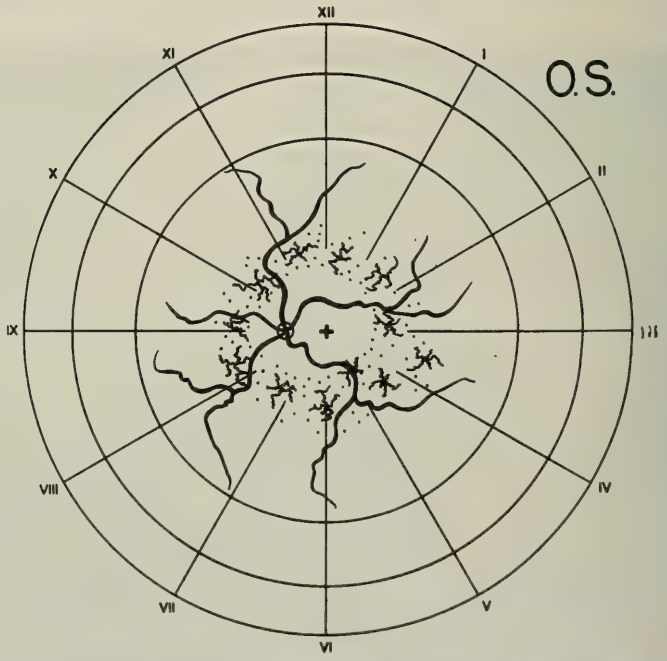


FIGURE 4b.—*However, severe neovascular retinopathy was found in all other areas of the posterior pole in this patient. Several other patients had similar findings.*

FIGURE 5a.—*Diffuse angiopathy with leakage from neovascular patches before treatment by laser photocoagulation.*

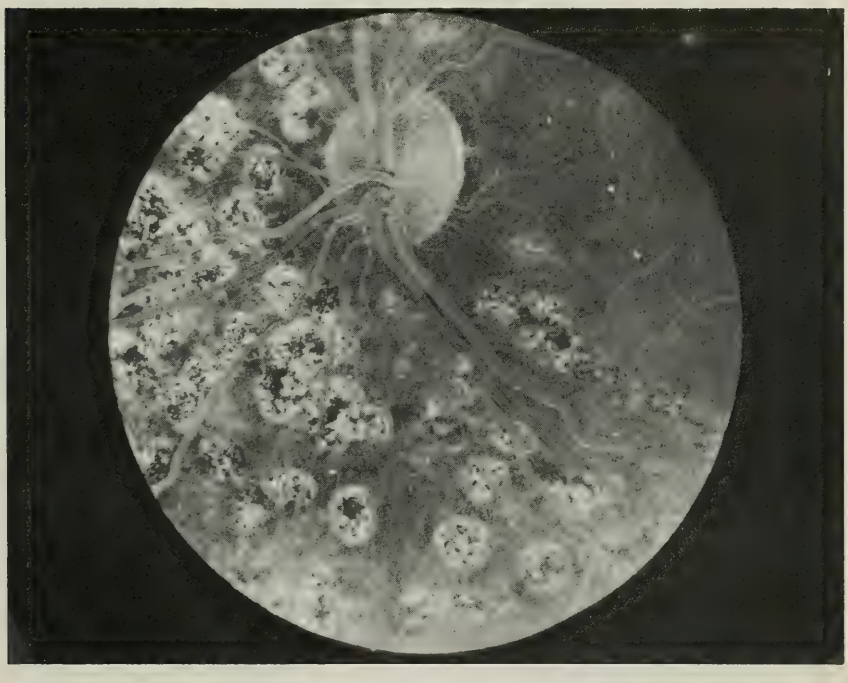
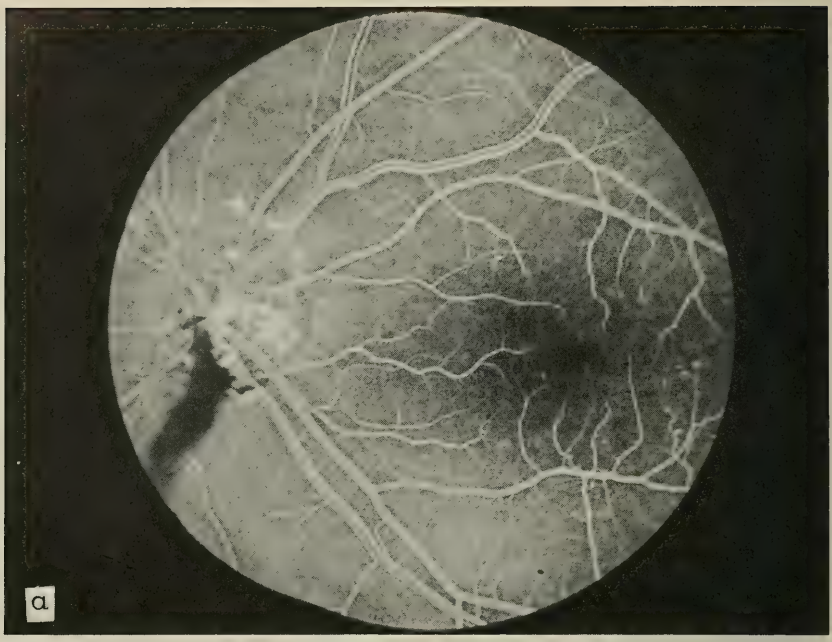


FIGURE 5b.—*Decrease in diffuse angiopathy and in "leakage" 6 months after treatment. The usual laser lesions showed characteristic pigment clumping and atrophic areas which "light up" with the choroidal flush.*



(*Arteriovenous phase.*)

FIGURE 6.—*Group III classification: a and b show before treatment fluorescein appearance with disc leakage and frank hemorrhage* (*Venous phase below*).

(*Arteriovenous phase.*)

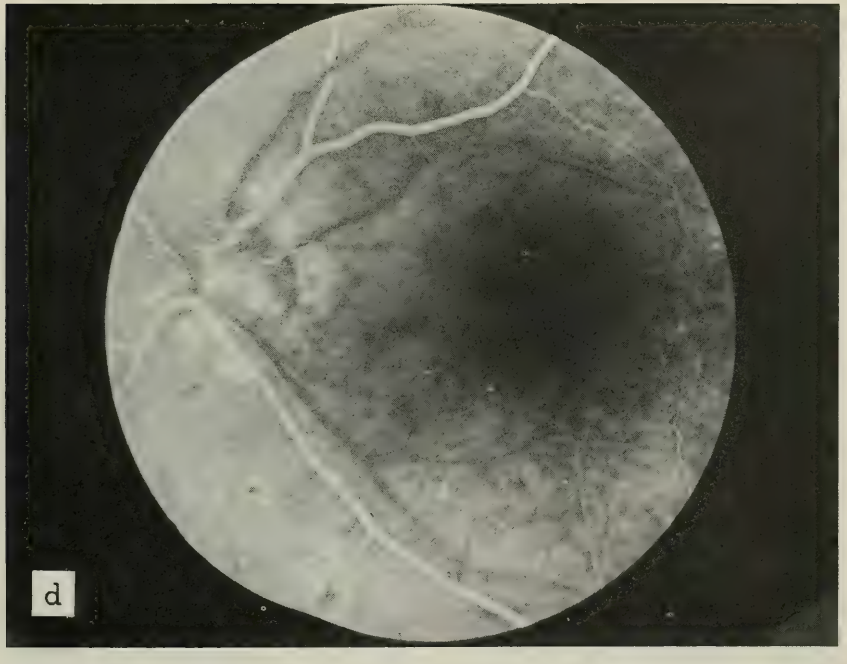


FIGURE 6 *c–d.—Eight months after completion of treatment, no new vessels are visible ophthalmoscopically, and on fluorescein there is a marked decrease in activity at the disc (Venous phase below).*

FIGURE 7.—*Severe diffuse angiopathy characteristic of group classification VI (DA 4).*

defects and without altering the vitreous if possible. The new vessels would not necessarily have to be attacked directly unless bleeding was imminent. The ruby laser emission has primary absorption in the pigment epithelium with most of the destruction in the deeper layers of the retina. In practical usage with grade II and III lesions, the nerve fiber layer remains intact so that sector defects do not occur. Further, the 2.5-degree (0.75 millimeter) burns are small enough to permit summation such that localized scotoma have not been plotted by 3 millimeter per 1,000 or 3 millimeter per 330 testing. Flicker fields and dark adaptation studies have been contemplated but not yet done.

It is true that grade IV lesions with retinal and vitreous hemorrhage may be produced with the use of this pulsed laser. The inexperienced are certain to produce these lesions particularly in the diabetic. During our first 2 months, we had two serious grade IV lesions which may have adversely affected the progression of the retinopathy. Four others were small preretinal hemorrhages and had no deleterious effect. By careful observation of the changing pigmentary character of each retina, by adjusting for the variations in retinal thickness, and by avoiding retreatment in areas of fresh lesions, these grade IV lesions have been avoided.

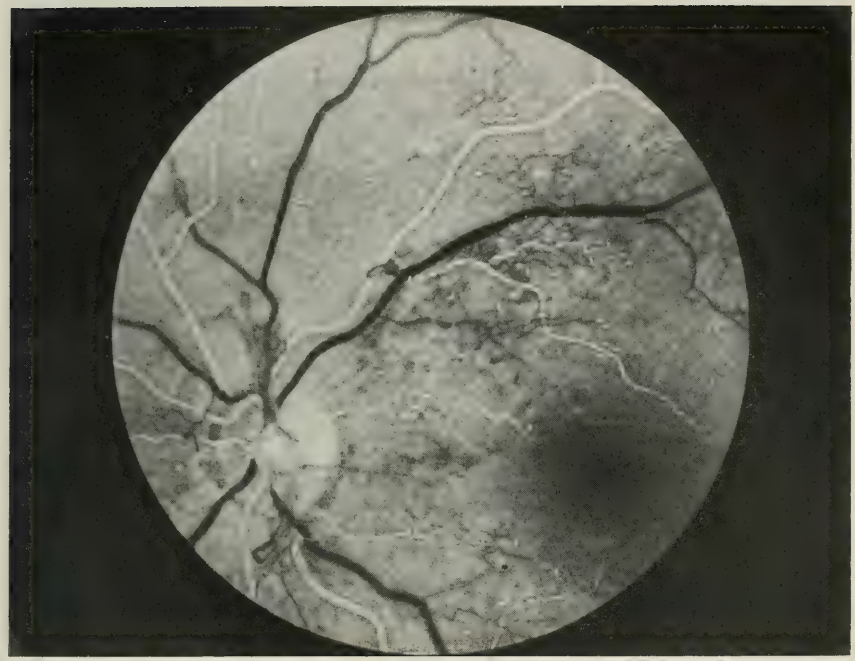


FIGURE 8a.—*The multiple small clusters of "new vessels" on or in the retina, radiating from disc area especially along the superior temporal vein, are seen on background of the choroidal flush in the arterial phase.*

FIGURE 8b.—*The "new vessels" start to fill in the relatively late phase without diffuse "leakage".*

FIGURE 9.—*Characteristic fluorescein pattern of elevated rete at disc with extensive "leakage" of dye.*

The nature of the ruby light (size of parallel beam and absorption characteristics) decreases the hazards to media (at the energy levels used). Postoperative vitreous traction has never been related to the treatment per se. No cases of iritis, cataract formation, or alterations of intraocular pressure have been detected. In a few cases (not tabulated) pigment specks have been seen scattered on the anterior surface of the iris near the sphincter. However, iris atrophy and pupillary abnormalities have not been observed. Once the burn has been placed, no early or late postoperative complication ensues to our knowledge. No hemorrhage has occurred during the first postoperative week and no hemorrhage in the postoperative period (early or late) could be attributed to the treatment. In general, then, the ruby laser photocoagulation treatment has advantage, particularly in regard to the approach described in this report.

The section on ophthalmic results has detailed the effects of treatment in specific areas. In general, it is our impression, on the basis of clinical observations and fluorescein angiographic studies, that there has been definite and probably beneficial effect on the arterial-capillary-venous vascular balance of the retina. Neovascular nests even at the disc have disappeared or become nonfilling. Diffuse angiopathy in the disc-macular area has improved. Blotches and red dots have

become much less numerous. Edema has subsided. Discs have appeared paler. Fibrous proliferation has not been affected. And most interestingly, we have the distinct impression that the major veins have become less dilated, less tortuous, and even perhaps less "leaky." These favorable changes in this short-term period encourage us to undertake treatment of the earlier cases of diabetic proliferating retinopathy with the hope that, by producing a compensated state, the later stage can be at least delayed or even arrested—without the need to resort to more drastic xenon photocoagulation or pituitary ablation. The shortened life expectancy of patients entering the neovascular phase makes this technique of inducing arrest plausible and attractive—leaving the patient more intact visually and medically. Of course, more followup time is mandatory.

If indeed this hypothesis and its technique proves effective, the mechanism of action remains at best unclear. Retinal tissue is being scarred and destroyed, perhaps reducing total retinal metabolic demand. Favorable responses with little treatment in patients with obliterated arterial channels (arteriosclerosis) and neovascularization suggests there is a critical factor here. However, fluorescein angiography and electron microscopic studies (*14*) of laser lesions may point to more basic alterations of the capillaries themselves.

Two disturbing thoughts occur. Is it possible that we can obtain a temporary state of compensation from which further progression of diabetic proliferating retinopathy may suddenly occur? Then do we have a scarred retina that cannot be further treated? Would then pituitary ablation be possible? If the recurring neovascular process is not generalized, of course, then localized xenon or "green" laser photocoagulation would be useful. Parenthetically, we do feel that a "green" laser or xenon would be useful in "ruby" laser treated eyes that have elevated vascular patches with appearance of impending hemorrhage. Second, is it possible that overtreatment could induce a slowly progressive retinal and optic atrophy and its attendant visual loss? If such a process were possible, the shortened life expectancy of these diabetic patients would limit this as a significant problem. Presently, there is not the slightest hint of this. However, we have had the impression of progressive and continuing improvement of the diabetic proliferating retinopathy as the interval after treatment increases, suggesting a continuing dynamic change.

CONCLUSION

The interesting and exciting hypothesis, that the progress of diabetic neovascular proliferating retinopathy may be favorably altered by

reducing the amount of functioning retina and thus possibly altering retinalchoroidal metabolic balance by producing small "harmless," nonfunctioning chorioretinal scars using the ruby laser photocoagulator, is being tested on a large group of diabetic patients. The favorable short-term impressions encourage us to continue and to enlarge this study in the hope that this planned selective destruction by photocoagulation may be used in the most efficient and scientific way possible. However, only the long-term outcome can truly judge the efficacy of the approach outlined in this preliminary report.

Acknowledgments

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CHAPTER 36

Photocoagulation Therapy of Diabetic Retinopathy

GILBERT W. CLEASBY, M.D.

The incidence of diabetes mellitus in the general population has been rising steadily in recent decades, mainly due to increased longevity and reproduction of diabetics. In addition, wider application of more sophisticated diagnostic techniques has resulted in discovery of more individuals in the large reservoir of undetected diabetics. Since the incidence of vascular complications of diabetes is related to duration of the disease, diabetic retinopathy is becoming a leading cause of new blindness in populations for which current statistics are available. It is estimated that approximately 19 percent of all blindness in the United States is caused by diabetes (*1*).

Many types of therapy have been utilized for treatment of this problem, including almost all known vitamins, hormones, and diets. Many types of hormonal suppression have also been tried including direct attacks on the pituitary in recent years. At the same time, ophthalmologists have begun attempting to control the retinal vascular disease directly by photocoagulation.

Although all presently available methods of controlling diabetic retinopathy leave much to be desired, there is reason to hope that their selective employment can maintain useful vision for many of these tragic patients for an indefinite period of time. It is also hoped that future more effective therapy, perhaps directed to the basic biochemical abnormality, will become available to help those patients who have survived and still have useful vision.

PATHOGENESIS

Diabetes mellitus is characterized by ultimate development of degenerative changes in blood vessels throughout the body. The basic abnormality seems to be one of altered permeability in the intima or basement membrane. The mechanism of this pathologic vascular alteration is not known, but it is believed that genetic, metabolic, immunologic, and hydrodynamic factors may all be involved. Although

Department of Ophthalmology; Presbyterian Hospital of Pacific Medical Center, San Francisco, Calif. 94115.

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there are many who believe that meticulous medical control of the diabetes with careful regulation of diet will retard the disease, the most significant factor associated with vascular complications is duration. Although a great deal of research has been done on the problem, the pathogenesis of diabetic retinopathy is not clear. Extensive work by Ashton (*2*), Cogan (*3*), Hogan (*4*), Bloodworth (*5*), and others has shown the early changes at the capillary level to include the following: loss of mural cells, endothelial proliferation, alteration of the basement membrane, occlusion, and development of shunt vessels.

PATHOPHYSIOLOGY

Although the onset and rate of progression of diabetic retinopathy varies greatly from individual to individual, and often demonstrates stationary or regressive phases, there is a characteristic sequence of events leading ultimately to loss of vision if the patient lives long enough (*6*, *7*). The progression of retinal disease can be generally divided into two phases, "preproliferative" ("nonproliferative") and "proliferative." The preproliferative phase typically begins with appearance of microaneurysms around and temporal to the macula, often accompanied by small intraretinal hemorrhages of the "dot and blot" type. These signs of circulatory disease are followed by fine "hard" exudates in the posterior pole, often forming a circular ("circinate") pattern around the vascular abnormalities. The exudates apparently represent inspissated residue of plasma lipid and protein material which has leaked through the damaged capillary and aneurysmal walls and accumulated in the outer plexiform layer of the retina. The basic circulatory incompetence also leads to retinal edema in the macular area, a much more common cause of reduced central vision in the preproliferative stage of disease than has been previously recognized. Marginal retinal nutrition in this situation leads to a stage of relative anoxia. As has been described by Michaelson (*8*) and by Wise (*9*), this may release a "vasoformative" factor responsible for attempted development of collateral vascular channels. This is evidenced clinically by neovascularization, as imperfectly formed new channels develop in the areas of marginal nutrition and spread across the retinal surface.

At the same time, focal areas of microvascular occlusion (microinfarcts) can lead to the development of "cotton wool" exudates and superficial flame hemorrhages, even in the absence of hypertension. This adds to the problem of circulatory insufficiency with increased anoxia and release of additional vasoformative factors. The spread

of abnormal new vessels across the retinal surface leads to reactive gliosis and development of attachments to the posterior cortical layer of the vitreous. This represents the intial phases of proliferative disease. As is well known, these areas of neovascularization can undergo spontaneous regression. Obliteration of these vessels is usually accompanied by additional gliosis, strengthening the bond to the posterior vitreous face. The initial retes of neovascularization tend to form selectively along the superior and inferior temporal venous trunks and around the nerve head. In older patients who have previously developed posterior detachment of the vitreous, neovascular adhesions to the posterior vitreous cannot develop, so the exudative component of the disease predominates with gradual accumulation of increasingly greater deposits in the macular area. As the microvascular changes progress, signs of the disease develop in larger vessels, particularly the veins. The veins often show tortuosity with beading and segmentation of the blood column. Characteristically, the retinal arteries show less change until late in the course of the disease, at which time nonspecific irregularity and increase of light reflex become apparent, along with occasional sheathing of smaller branches.

The proliferative phase of diabetic retinopathy, as described above, begins with the formation of "neovascular" channels and subsequent formation of reactive gliosis with adhesion to the posterior vitreous face. Subsequent vitreous contraction and posterior detachment results in traction on the new vessels, leading to recurrent hemorrhage. The new vessels are fragile and bleed easily as they are subjected to the stress of movements of the vitreous body. Adhesion of vitreous to retina tends to be focal in the areas of neovascularization. As the vitreous moves further forward, this leads to localized areas of traction type detachment. The retina often splits as it detaches, forming a type of retinoschisis. Further anterior movement of the vitreous results in additional hemorrhage and more extensive traction detachment. This, in turn, leads to additional gliosis. It was formerly thought that the proliferative retinovascular elements extended forward into the vitreous. However, it now appears well established that most proliferation takes place along the posterior viterous face, forming a "retrovitreal" membrane. This has recently been documented by histopathologic studies by Lee (*10*). The time needed for this stage to advance to total, "hopeless" detachment is unpredictable, varying from weeks to years. However, once this state has been reached, the outcome is usually only a matter of time. As mentioned, the development of traction detachment involves adhesion between retina and vitreous. Degeneration and anterior collapse of the vitreous body, particularly in young individuals, may be accelerated by the release of serum com-

ponents from incompetent retinal vessels in the organizing retrovitreal membrane.

The pathophysiologic mechanism might best be considered as a process of gradually increasing vaso-obliteration, leading to ischemia, followed by exudation and a vasoproliferative response.

INDICATIONS FOR TREATMENT

In the present state of knowledge there can be no hard and fast indications for treatment of diabetic retinopathy with photocoagulation or any other means. The problem may be approached by considering the situation from both the ocular and general standpoints. Specific ocular conditions which pose a threat to vision and which appear to call for treatment include the following: macular edema and exudate, recurrent hemorrhage, progressive proliferative retinal disease, and traction detachment.

From the overall standpoint, the decision as to whether or not treatment is indicated is influenced by the status of the other eye, a history of progressive ocular disease and visual disability, general health, and life expectancy.

In addition to the above mentioned factors, helpful information for evaluation of the situation can be obtained by fluorescein angioscopy and angiography (*11*). This test, when performed by an experienced observer, can provide important information on the state of circulatory incompetence in the eye and pinpoint foci of maximum vascular disease.

In summary, if diabetic retinopathy appears to be following a progressive course with increasing visual disability in a patient with reasonable life expectancy and in whom the foci of retinal vascular disease can be seen, treatment by photocoagulation appears to be indicated. As is customary in the exploratory phases of any therapy, treatment is usually reserved for advanced and desperate cases. However, as more time passes, more knowledge is gained, and more sophisticated means of detecting areas of focal deficiency are developed, it can be anticipated that photocoagulation will be applied to patients who have not yet reached a desperate situation in which they are faced with imminent loss of vision.

For the sake of completeness, it should be mentioned that consideration has also been given to treatment of the terminal stage of the disease; i.e., when advanced traction type retinal detachment has taken place. Work by Okun and Fung (*12*) has shown that there is reasonable hope for benefiting patients in this situation by performance of scleral buckling procedures.

TREATMENT TECHNIQUES

Examination

When the patient is first seen, a complete eye examination is carried out, since patients with diabetic retinopathy do have a high incidence of associated ocular diseases, such as cataract and glaucoma. A careful review of the medical and ocular history is also important. Information concerning the duration of disease, date of onset and rate of progression of visual disability, number of hemorrhages, inventory and exact dosage of all medications, family history, occupation, and name and address of general physician, are all important. A drawing of the fundus pathology is made and multiple documentary photographs taken, clarity of media permitting. Fluorescein angiography is performed in order to gain more information on the status of circulatory physiology and to pinpoint areas of maximum leakage.

Discussion

After the above-described studies, the situation is discussed carefully and at length with the patient and his family. Since these patients are usually diabetics of longstanding, they are generally more aware of the nature and prognosis of their disease than are patients with new ocular problems. With the aid of a model eye, the nature and anatomy of the disease is described. Discussion of prognosis is modified by the state of the disease and whether or not there has already been severe loss of vision in one or both eyes. The usual candidate for treatment has far-advanced disease and is well aware that he faces ultimate blindness if he lives long enough. He is told that the aim of photocoagulation is to destroy abnormal blood vessels in order to stop and/or prevent bleeding and to bring the disease process to a state of arrest or quiescence with preservation of central vision. It is also pointed out that photocoagulation of itself carries some hazard and will result in loss of peripheral vision (to a variable degree), reduction of color perception, and reduced adaptation to changes in illumination. In addition, it is emphasized that treatment cannot be guaranteed to accomplish its purpose, but is done as a stopgap measure to attempt preservation of central vision for an indefinite period of time. It is also mentioned that the future may bring new and more effective means of dealing with the problem. In outlining the protocol to be followed, the patient is told that usually two or more treatment sessions must be carried out over a period of months. If the disease is bilaterally symmetrical and both eyes have reasonably good central vision, it is

proposed that one eye be treated and that the other be kept as a control. The decision as to which eye should be treated can be based on the level of central vision, the extent of the disease, and the fluorescein angiography pattern. If the patient appears to understand the situation and wishes to proceed, arrangements are made for photocoagulation. For the younger patients with longstanding diabetes, discreet inquiries are made to determine whether or not they are aware of the general situation concerning longevity and genetics associated with their disease. Only in those few who appear to be poorly informed, does there seem to be any point in carrying out extensive discussions along these lines. It is generally preferable to leave this in the hands of the general physican.

Procedure

The patient is hospitalized. In order to avoid problems with regulation of the diabetes, specific orders are written to prevent the patient from being placed on an "NPO" status.[2] Following the usual preoperative sedation and analgesia, he is taken to the operating room. After institution of topical anesthesia with multiple drops of 0.5 percent proparacaine hydrochloride, a retrobulbar injection of 4 cubic centimeters of 2 percent mepivacaine hydrochloride (Carbocaine) is given. An injection of fluorescein is given in the antecubital vein, using either 10 cubic centimeters of 5 percent solution or 5 cubic centimeters of 10 percent solution. Detailed repeat fundus study is carried out by the binocular indirect ophthalmoscope, with and without the Wrattan No. 47 filter. Focal areas of staining are used as a guide to begin therapy.

The patient is positioned in proper relationship to the Zeiss xenon photocoagulator and a lid speculum placed in the eye to be treated. A pilot application is made to one of the focal areas of vascular disease, usually along the superior temporal vascular trunk. The effect is evaluated and any necessary adjustments made in settings of the photocoagulator. Following this, light applications are placed along all major vascular trunks to all detectable areas of vascular disease, swinging temporally around the macula and nasally around the nerve head, taking care to spare the fovea, papillomacular bundle, and nerve head. Treatment is aimed at new vessels on the surface of the retina concentrating on juxtavenous sites. Only a single application is placed on a given focus. (Retreatment of a previously treated site may be done in followup months if there is evidence of residual or recurrent vasculopathy.) Even with a cloud of fluorescein as a background screen, markedly elevated tufts of vessels show little visible response. Minimally

[2] Nothing by month.

elevated vessels, however, do seem to be occluded immediately by the coagulative reaction. Attention is directed to locations where markedly elevated vessels arise from the retinal plane. Although I avoid the disc, I do not hesitate to place minimal applications up to the nasal margin. Treatment is monitored with the binocular indirect ophthalmoscope. Frequent study of the fluorescein staining pattern is done to be certain that all major foci of vascular disease are treated. When treatment has been completed, corticosteroid and atropine ophthalmic ointments are instilled and a pad applied. The following morning, fundus and slit lamp examinations are performed. If there is no evidence of complication or adverse reaction, the patient is dismissed from the hospital with instructions to return to the referring physician and to continue using a cycloplegic drop and corticosteroid ointment for at least 1 week. A date is made for the patient to return in approximately 2 months for followup observation and possible additional treatment, assuming no interim problems. If extensive treatment has been performed, the patient is warned that he will have severely decreased vision for approximately 2 weeks, but that he need not limit his activities except for restrictions imposed by reduced vision. A complete report is sent to the referring ophthalmologist with a copy to the general physician.

Assuming reasonable clarity of media, the initial photocoagulator settings are: Basic intensity, I; iris diaphragm, 2.0 units; field diaphragm, 4.5 degrees. A visible reaction around the treated vessels is usually obtained within one-half second. If these settings are not adequate, I prefer to increase the basic intensity to II or III. Only after this has been done do I consider opening the iris and field diaphragms. If the pupil cannot be dilated widely, I believe it is important to keep the iris diaphragm partially closed in order to minimize the effects of heat on the anterior segment. Only rarely is it necessary to use the high intensity range.

Maximum pupillary dilatation is so important that I occasionally use subconjunctival injection to supplement the effect of topical agents. Special efforts are made to maintain corneal clarity. Frequent installations of saline usually suffice. Treatment of disease in the aphakic fundus or to areas of elevated proliferative disease can often be augmented by interposing a plus spherical lens in the beam pathway.

EFFECTS

Once diabetic retinopathy has entered the proliferative phase, one can predict that it will probably reach an ultimate stage of regression

if the patient lives long enough. Unfortunately, the visual elements of the central retina are usually severely damaged or destroyed by that time. In some patients, particularly the older group, the process remains indefinitely in the pre- or non-proliferative stage. Visual disability in these patients usually begins initially with macular edema, followed in a variable period of time by the appearance of "hard" exudates. These exudates appear to cluster selectively in the outer plexiform layer around the fovea. Their presence leads ultimately to cystic degeneration and gliosis with irreversible loss of central vision. The aim of photocoagulation is to destroy abnormal new vessels around the posterior pole in order to arrest and reverse the secondary effects on the macula and to induce a state of remission in the vascular disease generally. A sufficient number of cases have been treated and followed over a period of time to determine that this does actually take place. (Incidentally, this effect can also be seen following photocoagulation of other vascular diseases, such as Coats' disease, Von Hippel's angiomatosis, and Eales' disease. As described by Michaelson (*8*) and Wise (*9*), the edema and exudate reflect a state of impaired nutrition and anoxia resulting from circulatory impedance. Anoxia appears to exert a vasoproliferative effect, leading to the formation of abnormal new vessels. The new vessels, in turn, exhibit abnormal permeability and fragility, leading to further extravasation of serum and blood. Destruction of these vessels, along with the associated retina, eliminates both the abnormal physiology and the abnormal anatomy. In addition to permitting resorption of edema and exudate, there often seems to be an arrest or reversal of the vasoproliferative cycle. It is possible that there is enough destruction of retinal tissue generally to decrease its metabolic requirements, further reducing the vasoproliferative stimulus. In addition, elimination of abnormal shunt and collateral vessels may result in improved circulation to the areas of untreated retina. In cases where macular edema is the proximate cause of reduced vision, there is often a pronounced improvement in vision as the edema clears in the weeks following treatment. "Hard" exudates clear more slowly. Unfortunately, glial scarring is often left following disappearance of the "hard" exudates. Fluorescein angiography is useful for documentation of improved circulatory physiology.

In addition to these general effects, there are specifice effects desired in the performance of photocoagulation for diabetic retinopathy:

Stopping of bleeding: As with any hemorrhagic retinopathy, photocoagulation of any detectable site of active bleeding is indicated. This, alone, would not be expected to have beneficial long term effects on the basic disease, but can be valuable in arresting the bleeding.

Creation of chorioretinal adhesions: Firm chorioretinal adhesions may act as an effective counterforce against vitreous traction on the retina.

Disruption of vitreoretinal adhesions: Elimination of actively growing and bleeding new vessels in areas of proliferative retinopathy seems to lessen and/or halt development of the vitreoretinal membrane which acts as a focus for forward traction as the vitreous body shrinks and collapses.

Treatment of focal retinal detachment: As the proliferative phases of diabetic retinopathy progress, focal areas of traction detachment often develop, characteristically along the superior and inferior vascular trunks. The forward traction from the vitreous often seems to result in a splitting of the elevated retina, forming a type of retinoschisis. In some cases, photocoagulation results in arrest or partial obliteration of these schisislike areas of traction detachment.

Prevention of rubeosis

Although it cannot be proved, elimination of abnormal new vessels in the retina may have a favorable effect on decreasing the incidence of rubeosis of the iris. Once rubeosis develops, the eye is doomed from the resulting anterior segment pathology.

It is interesting that there are a number of conditions occasionally associated with diabetic retinopathy which appear to exert a retarding effect on the course of the disease. One group has in common the effect of reducing arterial blood flow, similar to the effect of lowering water pressure in a defective hose. Advanced glaucoma (*13*) and carotid occlusive disease (*14*) both appear to have this type of protective effect. Another group of diseases is associated with reduced retinal nutrition. These include optic atrophy (*15*), high myopia (*16*) and severe chorioretinal scarring (*17*). The effects of these conditions on diabetic retinopathy generally coordinate with the postulated effects of photocoagulation.

COMPLICATIONS

Complications of photocoagulation have been gratifyingly infrequent. In my experience, there have been more problems involving the anterior than the posterior segment. Such complications include iritis with posterior synechiae, doubtless resulting from heat effects on the anterior uvea. Occasional vitreous and retinal hemorrhages, macular burns, and retinal detachments have been reported as a sequel to photocoagulation.

In the treatment of 87 eyes of 55 patients with a total of 196 photocoagulation sessions, there have been four cases of iritis. Three other patients have gone on to develop rubeosis of the iris. Wetzig (*18*) believes that hemorrhage occurring within 1 week of treatment and detachment of the retina occurring within 6 weeks of treatment should be listed as complications. Using these criteria, I have had one case of extensive intraocular hemorrhage and one case of traction detachment develop within the stipulated period following treatment.

In general, all patients who have had extensive treatment will suffer from some loss of peripheral field, deficiency of color perception, and reduced dark adaptation.

RESULTS AND PROGNOSIS

Results of therapy must be evaluated with the help of information available on the natural course of the disease. Although the clinical picture and usual distressing end results of longstanding diabetic retinopathy are well known to all ophthalmologists, there is a paucity of statistically reliable studies. Caird (*19*) in England has made careful and detailed observations on a large unselected series of untreated patients over a relatively long period of time. He has provided figures for the 5-year prognosis in the following categories:

Nonproliferative retinopathy with good vision: 14.5 percent blind; 35 percent with impaired vision.

Nonproliferative retinopathy with impaired vision: 50 percent blind.

Proliferative retinopathy at first observation: 50 percent blind; 36 percent with impaired vision; 14 percent with good vision.

One year after first vitreous hemorrhage: one-third blind; one-third with impaired vision; one-third with good vision.

Deckert (*20*) in Denmark has evaluated another prognostic factor in diabetic retinopathy. He and his associates found that there is a significant difference in prognosis between eyes which have localized peripheral proliferative retinopathy and eyes which have central proliferative disease. In those with peripheral disease, 50 percent were blind in 5 years. In those with central proliferative disease, 50 percent were blind in 2 years. Patz and colleagues at the Wilmer Institute have devoted attention to both the visual and systemic prognosis in diabetic retinopathy (*21*, *22*). A retrospective study of blind diabetic patients applying for guide dogs showed that the average life expectancy after onset of blindness in this group is 5.8 years. Patz's figures for the prognosis of proliferative retinopathy coincide closely with Caird's. Such patients with good visual acuity have a 50 percent chance of retaining good vision over a 5-year period. The remainder are either

blind or have severely impaired vision. Of great significance from the therapeutic standpoint, Patz's studies show that the majority of patients who become blind in one eye will become blind in the second eye within 1 year. The most significant recent short-term series is that of Davis (*6*, *7*). Of 65 eyes with proliferative diabetic retinopathy but without detachment followed for 6 months to 3½ years, 26 have been stable or showed regression (39 percent). Beetham (*23*) has continued his long-term studies of patients with diabetic retinopathy. His most recent figures for patients with proliferative retinopathy and good initial vision show that over a period of observation between 1 and 13 years, approximately 50 percent retained useful vision. This is somewhat more optimistic than the figures tabulated by other observers. However, of all his patients with proliferative retinopathy on first observation, only 34 percent had good vision when last seen.

The most significant data available concerning the treatment of diabetic retinopathy with photocoagulation have resulted from the pioneering work of Wetzig (*18*) and Okun (*15*, *24*). Of 123 eyes in 83 patients with a followup of 1 to 7 years, Wetzig reported the following results:

Stabilized: 62 percent.
Progression slowed: 20 percent.
Progressed without benefit: 18 percent.

In 50 patients with bilaterally symmetrical disease, Okun reported the results of treating one eye and leaving the other as a control. In 25 patients, there was no change of status of the disease in either eye. In the remaining 25 patients, definite progression of disease took place. Of these, the progression developed in the untreated eye in 23 and in the treated eye in two. His overall statistics indicate that the disease process was stable over the period of observation in 80 percent of treated patients and in 58 percent of untreated patients. He believes that these results are statistically significant.

Analysis of my patients who have had treatment with photocoagulation for diabetic retinopathy has been carried out. A total of 87 eyes in 55 patients have been followed between 6 months and 4 years. Seventy-three of the 87 eyes had proliferative diabetic retinopathy upon initial observation. Fourteen eyes were suffering from nonproliferative diabetic retinopathy. Following the criteria of Wetzig, the results have been analyzed as follows:

	Stabilized (percent)	Progression slowed (percent)	Progressed (percent)
All patients	78	8	14
Patients with proliferative disease	75	9	16
Patients with nonproliferative disease	93	7	0

Evaluation of visual results

PROLIFERATIVE DISEASE

	Final observation		
	Good vision (percent)	Impaired vision (percent)	Blindness (percent)
Initial good vision (20/20–20/50)	73	21	6
Initial impaired vision (20/60–20/200)	21	63	16
Initial blindness (20/200 or less)	4	16	80

NONPROLIFERATIVE DISEASE

Initial good vision (20/20–20/50)	100		
Initial impaired vision (20/60–20/200)		100	
Initial blindness (20/200 or less)		40	60

SUMMARY

Although photocoagulation as a therapy for diabetic retinopathy must be viewed as an interim measure, it is my belief that the currently available data support the evidence that it is definitely useful in slowing progression of the disease.

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CHAPTER 37

Light Coagulation in Proliferative Diabetic Retinopathy [1]

JOHN H. DOBREE, M.D., F.R.C.S.

This is an account of a comparatively small series of light coagulations for proliferative diabetic retinopathy. It includes every case in which the coagulator has been used in the condition, including the earliest attempts, often in unsuitable cases, over 4 years ago. However, every case has been photographed before operation and followed up by subsequent photographs so the mistakes in therapy as well as the benefits have been recorded.

RATIONALE OF TREATMENT BY LIGHT COAGULATION

Light coagulation has as its main aim the destruction of new-formed retinal vessels. This leads to four beneficial effects.

(1) Bleeding and the secondary effects of hemorrhage are prevented by obliteration of the new vessels.

(2) The further expansion of vascular arcades is prevented.

(3) The formation of cicatricial tissue in the later stages (stage III—see ch. 5) is lessened because the healed light coagulation areas consist of patches of choroido-retinal atrophy in which little or no connective tissue is present.

(4) Occasionally there may follow regression of new-vessel groups adjacent to those lying near a coagulated area.

CLINICAL MATERIAL

A total of 60 eyes have been light-coagulated. The results of 42 treated eyes are reported. A further 18 eyes have also been treated, but all these are recent coagulations with a followup of less than 5 months. There are 59 controls.

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[1] See appendix H for raw data on individual patients.

St. Bartholomew's Hospital, London, England.

TECHNIQUE

Anesthesia

The conjunctival sac is anesthetized by 1 percent amethocaine. A subconjunctival injection of either 4 milliliters of 2 percent lignocaine or 2 milliliters of 2 percent lignocaine with hyalase is used. In about one-quarter of the cases a general anesthetic has been used. In the cases where the lesions are small in number and not peripheral, a retrobulbar injection has not been found necessary.

Dosage of Light

The 4.5 aperture on the Zeiss coagulator using the "green II" setting is usually employed. Occasionally when lateral spread is undesirable the 3.0 aperture is used. Coagulations are usually limited to 75 per operation. Although the coagulating time varies with the degree of fundal pigmentation and other factors, it is helpful to have an approximate idea of the "total light energy" employed. It has been found that individual operators use different lengths of burst, and these recording devices may help to standardize the procedure. Until recently, the number of coagulations has been recorded on a click counter allowing the total time that the coagulating beam has been used to be recorded by means of a recorder built into the coagulator. A new device which records both the number of coagulations and total duration is in process of development.

Coagulation Technique

Coagulations are applied directly to the new-formed retinal vessels and the main arterioles and veins are avoided. In the case of vessels lying in the plane of the retina, each coagulation burst is continued until the choroid blanches. This has been found sufficient to destroy the new vessels. Coagulations are extended beyond the zone of new vessels, especially in treating fan-shaped formations.

In the case of new-vessel formations which extend forward from the plane of the retina, a greater light intensity is needed. Great care is taken that no large retinal vessels lie in the path of the beam.

Direct coagulation on the main retinal vessels or their branches is avoided. This is because sometimes in the natural evolution of the condition, there is an attenuation of the normal retinal vessels and a

hyalinization of some retinal arterioles (see ch. 5). It seems wrong, therefore, to do anything which may disturb the integrity of the retinal circulation.

Contraindications

New vessels on the disc

Several attempts have been made to coagulate vessels lying over the nasal border of the disc. These have been futile, probably because in an attempt to be as conservative as possible insufficient beam intensity and duration has been employed. Similarly, new vessels in the vicinity of the main trunks near the border of the disc in the 12 and 6 o'clock positions have been abortive. It is thought that with a more contracted beam of equal intensity, such as provided by the argon laser, it would be possible to pick off new vessels with minimal injury to nerve fibers.

New vessels in the vicinity of the macula

In a recent communication we stated that we felt it inadvisable to coaguate vessels lying within two disc diameters of the disc. More recent experience has, however, convinced us that certainly as regards lesions on the temporal side of the macula, it is safe to go much nearer, possibly as near as half a disc diameter if a narrow beam is used. On the two occasions where the macula and papillomacular bundle were accidently involved in a direct coagulation, we found that the resulting scotoma exactly coincided with the burn recorded on the fundus photograph; in other words the nerve fibers had escaped injury.

Coagulation of vessels on connective tissue bands

After one experience in which a retinal detachment immediately followed such coagulations, we have avoided this practice.

Repeat Operations

As the series proceeds, it is clear that there is little likelihood of obliterating all new vessels at one particular time.

There are two reasons for this. First, new vascular formations often develop throughout the duration of the hypertrophic stages (stages I and II, see ch. 5) of the condition. Secondly, at the edge of coagulated areas, secondary groups of new vessels sometimes arise often

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within 3 months of the coagulations. These have been described by Okun and Cibis (*2*). For this reason patients are warned that the initial procedure is not to be regarded as a "once and for all" operation, but that other coagulations may be required subsequently. So far the operation has had to be repeated in eight cases.

COMPLICATIONS OF LIGHT COAGULATION

Macular burns (two cases)

In both instances this was due to the operator losing his bearings. No case of macular damage caused by extensive coagulations to other parts of the fundus has been encountered. In one case the burn was just nasal to the macula, but despite this the original vision was maintained.

Arterial occlusion (two cases)

In one case the occlusion was complete and resulted in optic atrophy and secondary glaucoma. In this case several arterioles and venules of the second and third branchings were deliberately occluded in order to cause an ischemia of two large sectors of the retina which contained multiple areas of new vessel formations. After the coagulations the vision was maintained at its previous level of 6/18 for 4 weeks, but after this time the whole arterial tree gradually narrowed, the disc became pale, and the vision dropped to perception of light before the secondary glaucoma developed some 2 months later.

In the second case, the second (lower) branch of the superior temporal artery was accidentally included in a coagulation and partially occluded. This resulted in a large area of retinal edema involving the macula, but this eventually cleared and the vision returned to its former level.

Retinal detachment

This was apparently caused by coagulations placed on vessels lying in a retinovitreal band. This seemed to contract the band and caused a detachment which was apparent within 1 week.

Extension of retinoschisis

This occurred in a recent case (August 1968) not recorded in the tables. Extensive coagulations were applied to new vessels lying above an inferiorly located retinoschisis and within a fortnight a consider-

able extension of the retinoschisis occurred. Again the mechanism appears to have been contraction of the anterior layers of the retina which in this case contained much connective tissue.

Hemorrhage during operation (one case)

This followed a direct coagulation on a diseased vein. A subhyaloid hemorrhage was seen to appear and gradually increase in size. It was arrested by obliterating the tributaries peripheral to the bleeding point. This was the one and only time such an accident has occurred.

It seems remarkable that bleeding is evidently unusual from choroidal vessels despite the large channels which must be obliterated in the course of every treatment.

RESULTS

Out of the 42 eyes treated, 17 must be regarded as failures, but valuable lessons have been learned from them. Three failures are among the errors in treatment detailed above. The remaining 14 include seven unsuitable cases in which the lesions were too far advanced in that traction bands and late choroido-retinal effects already dominated the picture. The remainder were either inadequately treated (some of the early cases) or those which had untreatable disc lesions.

In terms of retention of vision at the time of the present review, 20 eyes (47.8 percent) have retained the vision that they had prior to coagulation but a further five are considered as favorable results. Of the controls, 21 out of 59 (35.6 percent) retained the vision they had at the initial examination. It is thought that the "5-year retention of sight" offers a better method of comparison but it will be several years before the results can be assessed on this basis.

CONCLUSIONS

From our experience in light coagulation it is clear that early treatment of the new-vessel formations is essential, and further that repeated coagulations are necessary as and when new foci appear. Better techniques are necessary before disc lesions can be adequately tackled.

It must be pointed out that these early attempts probably give an unduly pessimistic impression of the merits of the method. At the present time very few units are tackling the problem of P.D.R. either by light coagulation or by pituitary ablation. It follows therefore that these units attract a high proportion of advanced and otherwise difficult

cases, so we tend to tackle the problem at the wrong end. It is felt that the best way of improving the present results is by the repeated careful ocular screening of all diabetics, particularly patients in large diabetic clinics. For, if the new vessels can be eradicated or inhibited at an early stage, the secondary effects such as bleeding and cicatricial changes, which are the major causes of blindness, can be minimized, or in some cases eliminated.

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CHAPTER 38

The Role of Photocoagulation in the Therapy of Proliferative Diabetic Retinopathy [1]

GORDON S. HARRIS, M.D.
P. KENNETH RENTIERS, M.D.

The retinopathy of diabetes has become a major cause of blindness during the past 40 years (*1*), associated with the increased lifespan of diabetic individuals. Proliferative diabetic retinopathy (P.D.R.) is an enigmatic process, the causative basis being ill understood, the natural history variable and the therapy dissatisfying. Unfortunately, good medical management and blood sugar stabilization does not confer immunity to this condition. Until a firm etiological base exists from which to attack this disease process, treatment on an empirical basis is all that can be offered.

The various means of therapy of P.D.R. are legion, testifying to their relative ineffectiveness. The list of methods utilized includes vitamin supplements, lipotropic factors, androgens, estrogens, pituitary ablative procedures, and photocoagulation. All of these methods have their adherents and much enthusiasm has been generated for each method in turn. Some of the initial enthusiasm was doubtless due to failure to consider the characteristic remission which is a late feature of the natural course of the disease.

To be clearly understood the stages of progression of P.D.R. must be related to the detachment of the formed vitreous (*2*, *3*) and its association with neovascularization. The term "neovascularization" is at times a misnomer as it occasionally may refer to the dilatation of preexisting capillary channels. These new vessels become adherent to the posterior surface of the vitreous while they undergo a cycle of growth and regression. Even after regression the vitreoretinal adhesions at the sites of the neovascularization remain.

In the second stage of P.D.R. active vitreous contraction occurs, pulling the newly formed vessels passively forward. The new vessels may break, causing hemorrhage; or the vitreous may remain adherent to the retina, producing detachment. This is the blinding process of the disease.

After vitreous contraction is complete, a remission of the retinopathy may occur with a reduction in the number of retinal hemorrhages, de-

[1] See appendix I for raw data on individual patients.

From the Department of Ophthalmology, University of British Columbia, and the Vancouver General Hospital.

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crease in venous dilatation and beading, attenuation of arterioles and venules, regression of new vessels, thinning of the fibrous proliferations and clearing of vitreous hemorrhage.

In about 10 percent of cases (*2*, *4*) a complete spontaneous regression seems to occur independent of any preceding vitreous detachment.

Once vitreous contraction is complete the residual level of visual acuity becomes relatively stable. Photocoagulation is a method of treatment designed to limit hemorrhages and preserve visual acuity until neovascularization has terminated and vitreous contraction is complete. When first practiced, photocoagulation was largely directed only at actively bleeding vessels during active vitreous contraction. Presently it is common practice to burn any areas of flat neovascularization as they appear in the early stages of P.D.R., in an attempt to forestall hemorrhage during subsequent vitreous contraction. For some years Meyer-Schwickerath, Wetzig (*5*), and others have been going a step further and photocoagulating intraretinal hemorrhages and aneurysms so as to prevent the formation of neovascularization.

Photocoagulation may also be used with effect to tack down areas of retinitis proliferans and wall off localized detachments. The retinal detachments in diabetes are unique in that they are associated with very posterior holes. These are frequently not amenable to conventional buckling procedures but often can be treated using posterior sclerotomy and photocoagulation.

In assessing the results of any therapy in P.D.R. it must be remembered that about 35 percent of untreated individuals with P.D.R. will retain useful vision (20/40 or better) over long periods of time (*4*). It is against this baseline that therapeutic results must be measured.

It may take up to 5 years in the untreated case for P.D.R. to progress from the early stages to extreme disorganization (*4*). The 5-year survival rate among those discovered to have P.D.R. may be as low as 38 percent (*6*). Photocoagulation has received attention as a single means of preserving some visual acuity in those unfortunate individuals found to have P.D.R. for the remainder of their often short lifespan.

METHOD

The Retina Service of the University of British Columbia has seen and followed about 200 diabetics during the past 4 years. Twenty-nine of these patients have received photocoagulation to 41 eyes in the treatment of diabetic retinopathy. An additional seven patients who have undergone pituitary ablation, both at this center and elsewhere, have also been followed.

All patients have received a complete initial ophthalmologic workup including tonometry, fundus photography and retinal drawings. Fluorescein angiography has been used in some cases. Followup examination at regular intervals, generally every 3 months, has been used to permit adequate documentation. Patients considered as candidates for pituitary ablation first undergo a complete hospital medical workup.

To permit statistical evaluation, the ocular status was initially classified by a modified scheme after Okun and Cibis (*7*), later modified to the O'Hare Classification.[1] Control is based on the visual acuity, the degree of vascular and fibrous proliferation and the presence of vitreous hemorrhage.

The data have been collected in a format suitable for computer programing.

Only those patients seen between September 1964 and January 1968 have been included in this series. Patients treated since January 1968 have been excluded in order to allow at least a 6-month followup on all patients. In addition, patients who received photocoagulation following pituitary ablation were also not considered. The Zeiss xenon photocoagulator has been used in the treatment of all patients. All patients were admitted to hospital for treatment but were discharged the same day or the following day unless their retinopathy was very extensive. A green 1 setting was used in most patients unless cataracts or vitreous opacities required greater intensity. The iris diaphragm was kept wide open, and generally a 6° aperture was maintained.

RESULTS

In some patients photocoagulation has been found to be an effective way of destroying areas of neovascularization, stopping preretinal and vitreous hemmorhages and in sealing areas of retina threatened by vitreous traction. Photocoagulation was generally confined to the areas of neovascularization and was used even when these occurred near the disc margin. However, new vessels between the disc and the macula were avoided. Burns, on occasion were placed up to 0.5 millimeter from the fovea and in these patients, as well as in a surprising number of other patients, no subjective visual field defect was apparent. It was often found difficult to obliterate effectively new vessels at the disc margin, and on several occasions new hemorrhages were started within a day or two of the photocoagulation when this area was treated presumably as a result of vitreous contraction. Occasionally small retinal hemorrhages were seen following the photocoagulation burns but these, without exception, cleared spontaneously.

[1] O'Hare Classification, p. xxi.

In several patients vitreous contraction was noted within a day or two of photocoagulation. This was associated at times with increased bleeding. On occasion, burns were made through dense areas of preretinal hemorrhage in order to stop persistent bleeding. This was often surprisingly successful; and areas of dense hemorrhage, measuring several disc diameters in size and which had been followed for months, were found to have completely disappeared within several days following treatment.

Localized retinal detachments, particularly if in the midperiphery, were sometimes surrounded by coagulation to prevent further detachment. This was not always successful.

Approximately 12 diabetic patients in the total series had associated rhegmatogenous retinal detachments. These were usually posterior detachments related to very posterior holes. It was felt that conventional buckling procedures, particularly with equatorial encircling tapes or implants, were not necessary or logical; therefore, these patients were merely treated with a posterior sclerotomy plus photocoagulation to the offending hole. In patients who showed vitreous traction which did not allow the retina to flatten after release of subretinal fluid, an imbricating procedure after the method of Custodis was used. The results in these treated cases were very good with a cure rate comparable to the results in rhegmatogenous nondiabetic patients.

The 14 eyes subjected to pituitary ablation did not fare as well. Eight of the 14 eyes (57 percent) maintained a stable level of visual acuity during a 24 month average survey (table 3).

Another group of eyes cannot be reported on because distance does not permit adequate followup.

DISCUSSION

Seventy-one percent of the treated eyes remained morphologically stable over the period of observation and the visual acuity remained as good or better in 72 percent of the treated eyes (table 2). Of the seven patients who received pituitary ablation, eight out of 14 eyes (57 percent) maintained a stable level of visual acuity (table 3). However, this number is too small for statistical evaluation. Okun and Cibis (*7*), using photocoagulation, cited a similar level of morphological (72 percent) and visual (73 percent) stability using the older classification over a comparable followup period (table 4). Wetzig and Jepson (*8*), using slightly different criteria, claim a 60 percent stability (table 4).

TABLE 1.—*Progression in proliferative diabetic retinopathy: treated eyes*

Initial classification	Eyes	Final classification				Followup (months)	Morphological stability (percent)
		I	II	III	IV		
I	13	8	1	1	3	16.0	64
II	16	2	10	2	2	16.0	75
III	8			7	1	22.0	86
IV	3				3	20.0	33
Total	40					17.5	71

TABLE 2.—*Change in visual acuity: treated eyes*

Initial classification	Eyes	Final classification			Followup (months)	Visual stability (percent)
		VA ↑	VA ↓	Same		
I	15	7	3	5	16.0	79
II	17	5	6	6	16.0	64
III	8	1	1	6	22.0	87
IV	3	2	2	1	20.0	33
Total	43	15	12	18	17.5	72

TABLE 3.—*Pituitary stalk section (Average followup 2 years)*

	Eyes	Percent
Stable VA	8	57
Decreased VA	6	43
Total	14	

TABLE 4.—*Photocoagulation results*

Study	Number of eyes	Followup	Visual stability (percent)
Okun and Cibis (*7*)	76	17 months	73
Wetzig, Jepson (*8*)	81	1 to 5 yrs	60
Rentiers, Harris	43	17 months to 4 yrs	72

TABLE 5.—*Pituitary ablation results*

Study	Method	Number patients	Followup	Visual stability (percent)
Pearson (*11*), Ray (*12*)	Hypophysectomy	56	3 months to 10 years	79
10 authors (*10*) (Sprague)	All 3	134	Up to 6 years	63
Rucker (*9*)	Stalk section	33	Over 1 year	64
	Control	33	Over 1 year	36
Rentiers, Harris	Stalk section, radiation	7	Average 24 months	57

It is very obvious to surgeons treating some patients with proliferative diabetic retinopathy that definite benefit occurs. An example of this is seen in the patient who has recurrent hemorrhages from a localized area of neovascularization over a period of months or years. Following successful photocoagulation the hemorrhage stops and never recurs again from this area. Areas of flat neovascularization, not located around the disc or in the macular area, can generally be treated without much risk and with reasonable hope of success. The more elevated the neovascularization, i.e., the more blood vessels have been dragged into the vitreous by the retinitis proliferans, the more difficult it is to obliterate vessels and the more likely one is to produce a vitreous hemorrhage. Not uncommonly one sees contraction of the vitreous after intensive photocoagulation—often within 24 hours. Neovascularization around the disc has shown more tendency to hemorrhage postoperatively and of course is associated with much more damaging effects on the visual field.

Field defects can vary from a complete altitudinal hemianopia (fig. 1) when extensive photocoagulation is performed along one border of the optic nerve to a localized scotoma confined only to the treated area (figs. 2–4). Wedge-shaped sector defects are not uncommon (figs. 2, 5, 6) and occasionally skip areas of field defect are produced when a photocoagulation burn has destroyed some but not all of the centripetal fibers passing in the neurofibril layer. Surprisingly, very few of the patients are aware of the field defects and relatively few are troubled by them. No patients in this series have received direct macular burns.

Once photocoagulation treatement has commenced, patients have to be followed closely. Additional areas of neovascularization or areas of localized hemorrhage must be treated promptly and often three, four, or five separate treatments may be required in each eye.

Complications have been few. Three patients had vitreous hemorrhages following treatment. All but one of these cleared. One patient developed an orbital hemorrhage following a retrobulbar injection of anesthetic. This was in a badly diseased eye and temporary occlusion of the central retinal artery occurred for about 30 seconds. The patient's vision was decreased for several days but now has returned to its normal level. However, the optic nerve appears somewhat paler than it had previously.

SUMMARY

Forty-one eyes in 29 patients have received photocoagulation over a 3½-year period. Visual stability has been achieved in 72 percent and

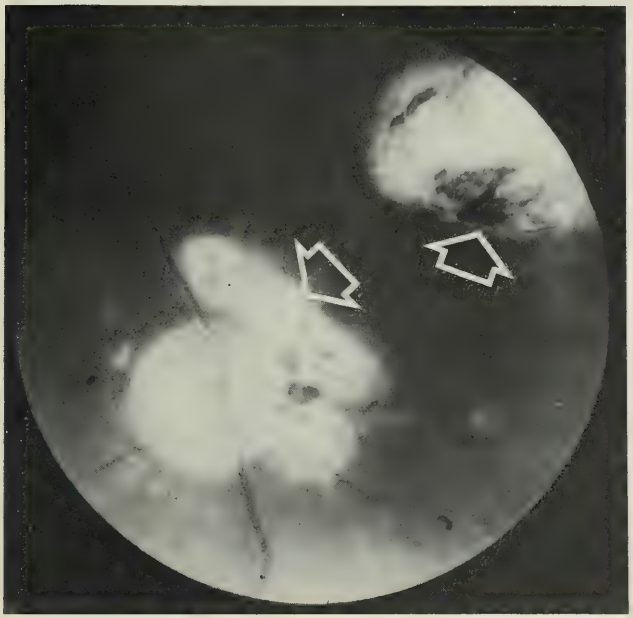

FIGURE 1.—*Left eye: Areas of photocoagulation along supero-temporal border of left disc and in left upper midperiphery.*

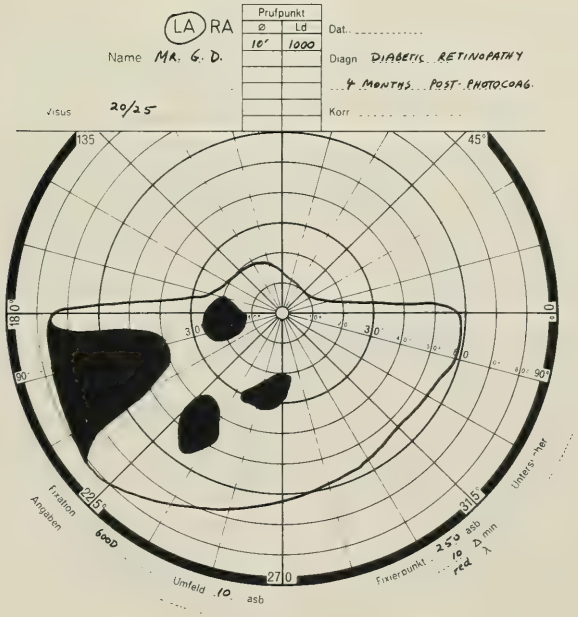

FIGURE 2.—*Field defects associated with photocoagulation burns in figure 1. Note altitudinal hemianopia, localized scotomata and sector defect.*

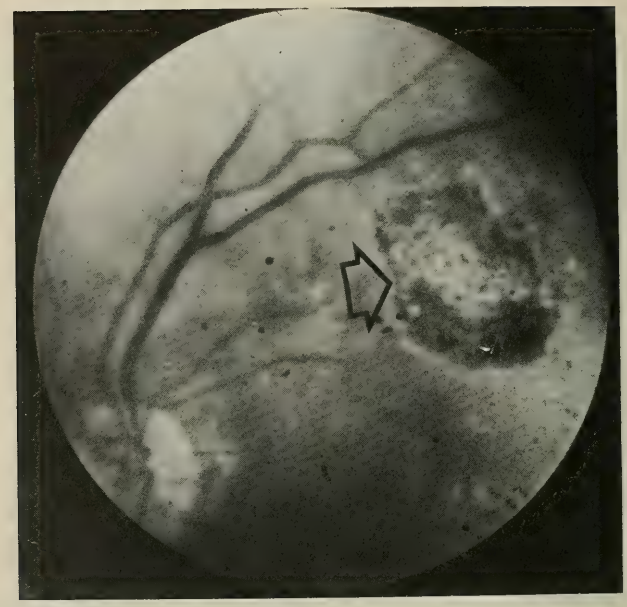

FIGURE 3.—*Photocoagulation burn to paramacular arc of 65-year old diabetic.*

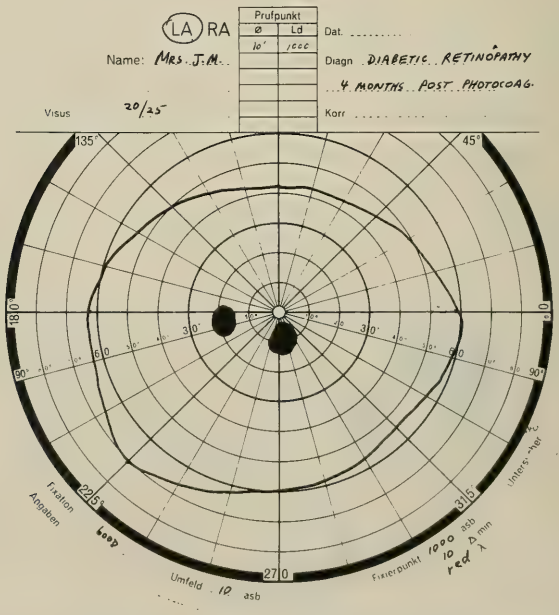

FIGURE 4.—*Visual field defect (scotoma) produced by photocoagulation as shown in figure 3.*

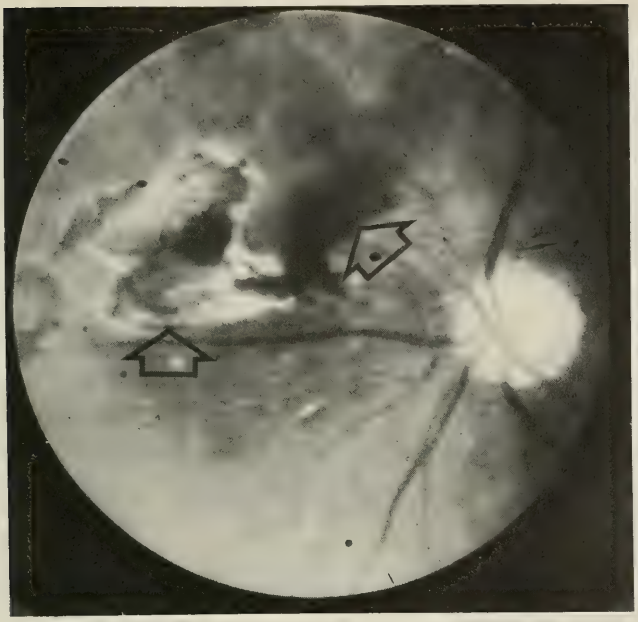

FIGURE 5.—*Photocoagulation burn to area of neovascularization near right disc. Some hemorrhage remains (arrow near disc). Visual acuity 20/25.*

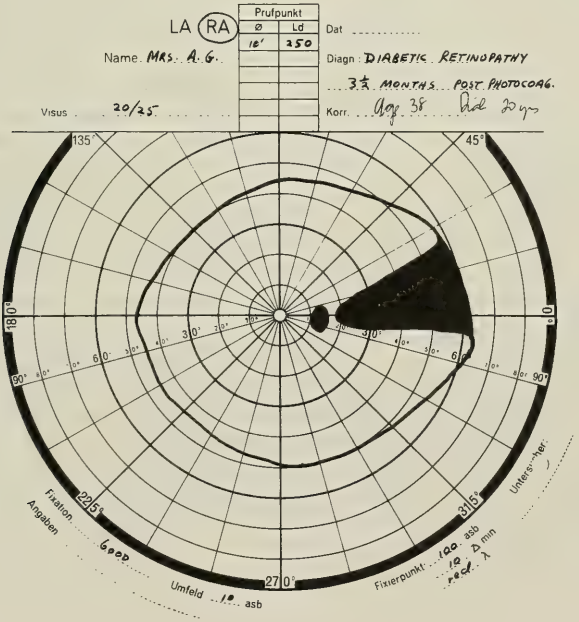

FIGURE 6.—*Visual field defect (sector) from photocoagulation as shown in figure 5.*

morphological stability has been obtained in 71 percent of the eyes. Results are best obtained when areas of flattened neovascularization are treated away from the macula and optic nerve head. Several types of visual field defects may be produced but surprisingly enough are not usually disturbing to the patient. The effects of any form of treatment, be it pituitary ablation or photocoagulation, have to be considered in the light of the natural history of the proliferative diabetic retinopathy and the forbidding outlook for life in these unfortunate patients.

Acknowledgment

We wish to thank the Photography Department of Shaughnessy Hospital for its help and cooperation.

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CHAPTER 39

Photocoagulation in Proliferative Diabetic Retinopathy: A Preliminary Report

HANS-WALTHER LARSEN, M.D.

During the last few years quite favorable results of photocoagulation have been reported in proliferative diabetic retinopathy (*1–9*), all using the Zeiss light-coagulator introduced by Meyer-Schwickerath in 1954 (*10, 11*).

Encouraged by these results, a series of photocoagulation treatments on diabetics with proliferative diabetic retinopathy were started at the University Eye Clinic (Rigshospitalet) in Copenhagen.

MATERIAL AND METHOD

The series consists of 39 diabetics (46 eyes), all presenting proliferative diabetic retinopathy. The photocoagulation was performed under local anesthesia using 2 percent lidocaine, retrobulbar. The pupil was maximally dilated before each treatment. The Zeiss light-coagulator was used and from five to 20 photocoagulation burns were applied at each treatment. The number of treatments varied from one to five at intervals from 2 to 3 months.

At first, overload power 1 to 2 with an aperture of 1.5 to 3.0 was used, without filter, but later normal power with apertures of 3.0 to 6.0 was used. The small aperture was preferentially used for making photocoagulation burns at the disc, while the other apertures were used in the fundus periphery. In all instances macular burns were avoided.

Practically none of the patients were hospitalized, but they were advised to remain in bed the first day after treatment and to limit their physical activity for approximately 1 to 2 weeks.

The series was divided into five groups. Group 1 comprises eyes with: Neovascularization extending from the disc and lying just prepapillary or peripapillary, containing only a delicate supporting stroma (figs. 1–2). Group 2: Peripapillary neovascularization extending into vitreous and containing a visible supporting stroma (figs. 3–4). Group 3: Neovascularizations outside the disc area located just preretinally and without any visible connective tissue (figs. 5–6). Group 4: Preretinal neovascularizations outside the disc area, containing a

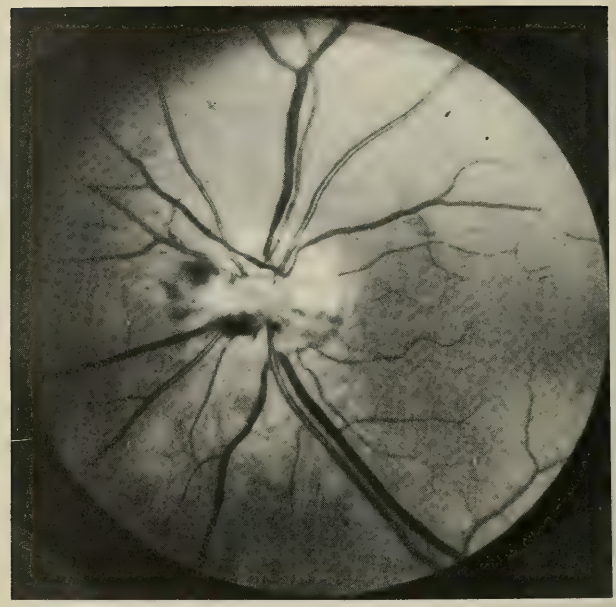

FIGURE 1

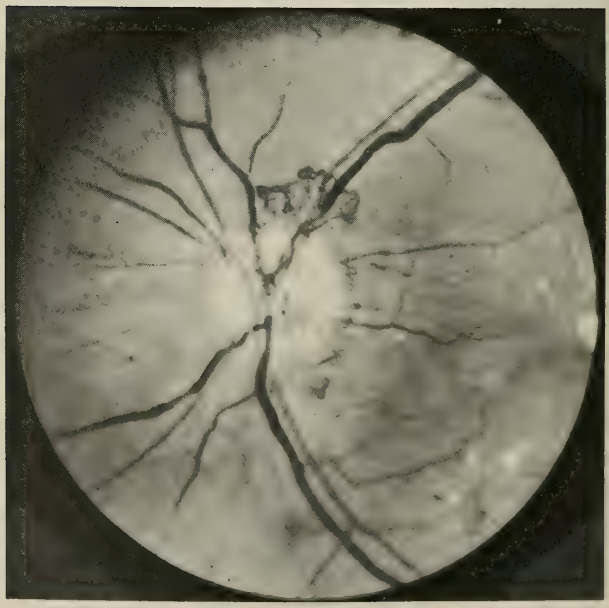

FIGURE 2

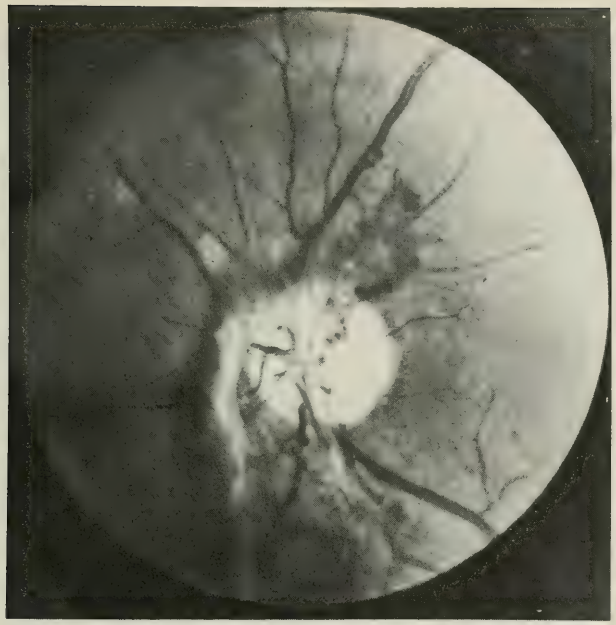

FIGURE 3

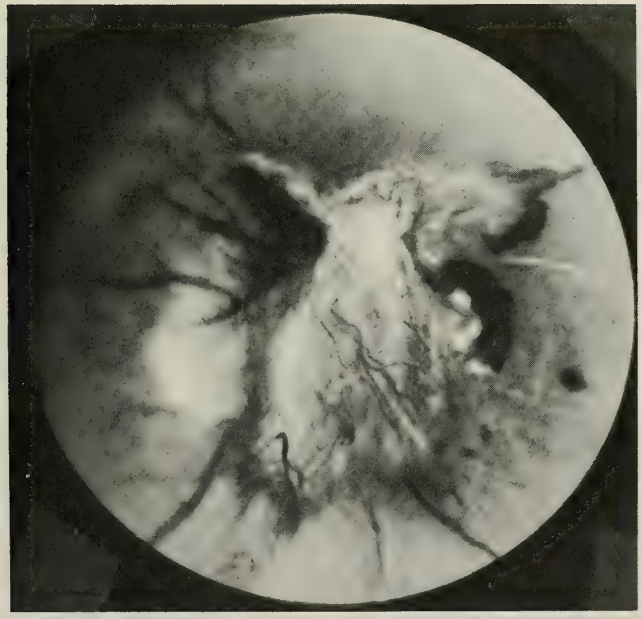

FIGURE 4

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FIGURE 5

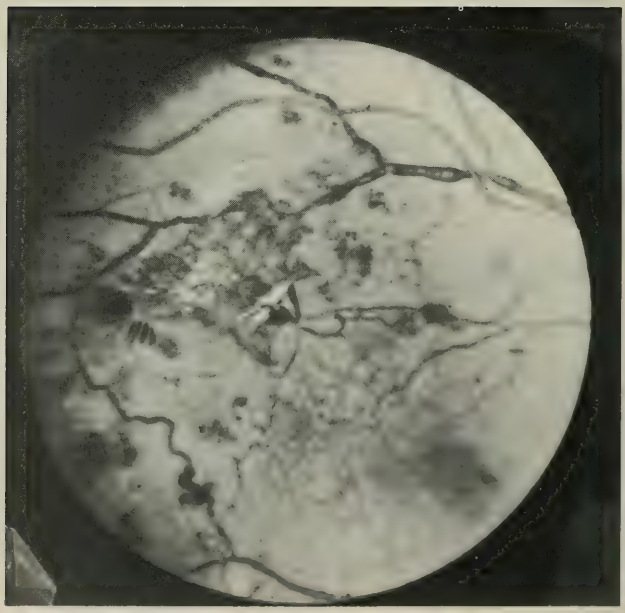

FIGURE 6

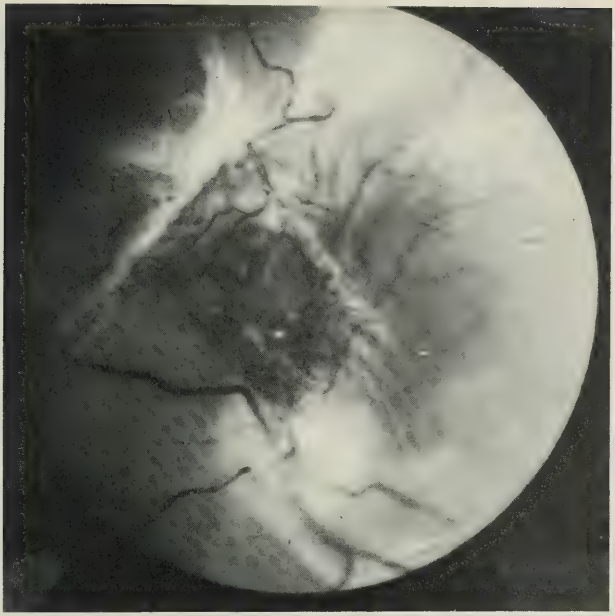

FIGURE 7

certain amount of fibrous tissue. Group 5: Cases with extensive fibrous tissue formation (fig. 7), pronounced degeneration of the hyaloid membrane (fig. 8), and vitreous collapse and retrovitreal hemorrhage (fig. 9).

The O'Hare Classification [1] was used in all cases.

RESULTS

The results of photocoagulation in group 1 are listed in table 1, and fundus photographs from a patient in this group, before and after treatment, are shown in figures 10 and 11.

The results of treatment in group 2 are listed in table 2.

The results of treatment in group 3 are listed in table 3, and fundus photographs from a patient in this group, before and after treatment, are shown in figures 12 and 13.

The results of treatment in group 4 are listed in table 4, and fundus photographs from a patient in this group, before and after treatment, are shown in figures 14 and 15.

All six cases in group 5 were failures.

[1] O'Hare Classification, p. xxi.

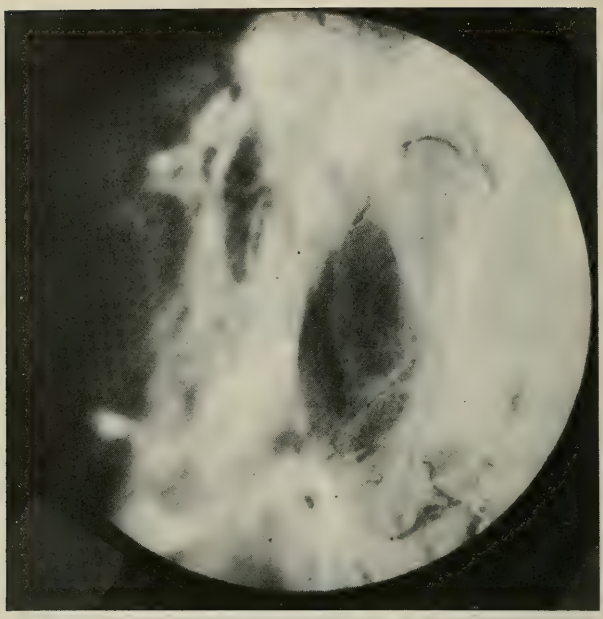

FIGURE 8

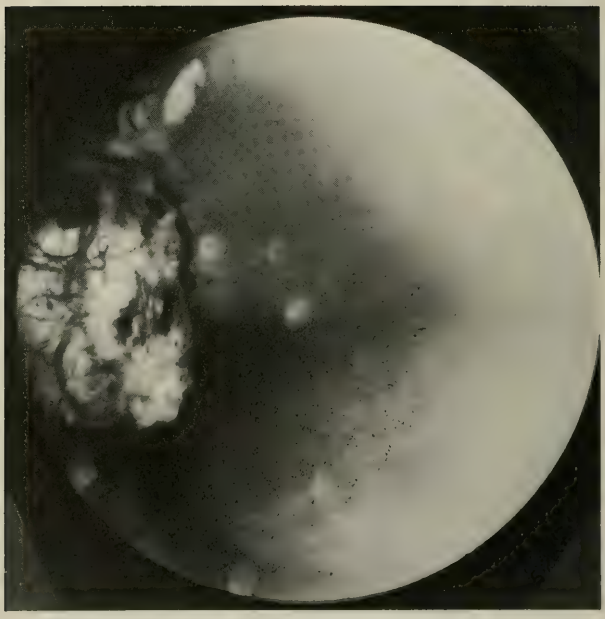

FIGURE 9

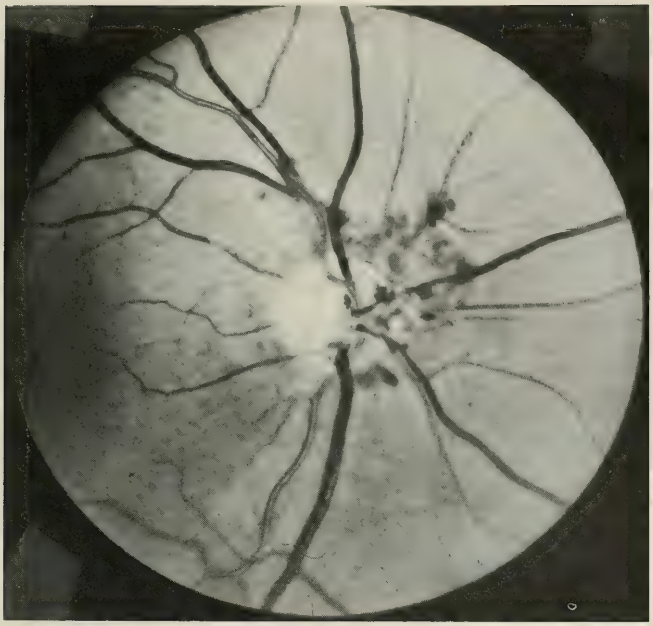

FIGURE 10

TABLE 1.—*Average age, 48 years; average duration of diabetes, 25 years*

Age	Sex	Age at diagnosis of diabetes	Age at 1st ocular symptoms	Visual acuity prior to photocoagulation	Classification of retinopathy prior to treatment	Followup period in months	Visual acuity at last examination	Classification of retinopathy at last examination
38	M	8	37	6/6	$N_1F_1H_0$	14	6/18	$N_0F_0H_0$
49	F	33	49	6/18	$N_2F_0H_0$	8	6/12	$N_0F_0H_0$
58	M	36	55	6/12	$N_1F_0H_0$	13	6/9	$N_0F_0H_0$
47	M	12	46	6/18	$N_1F_0H_0$	18	6/60	$N_0F_1H_0$
56	M	26	56	6/6	$N_1F_0H_0$	8	6/6	$N_0F_0H_0$
46	F	12	40	6/9	$N_1F_0H_0$	8	6/9	$N_0F_0H_0$
46	M	31	45	6/6	$N_1F_0H_0$	15	CF	H_2
51	M	23	51	<6/6	$N_1F_0H_0$	19	6/6	$N_0F_0H_0$
59	M	40	58	6/12	$N_1F_0H_0$	8	6/9	$N_0F_0H_0$
34	M	15	32	6/24	$N_1F_0H_0$	11	CF	H_2

TABLE 2.—*Average age, 46 years; average duration of diabetes, 23 years*

Age	Sex	Age at diagnosis of diabetes	Age at 1st ocular symptom	Visual acuity prior to photocoagulation	Classification of retinopathy prior to treatment	Followup period in months	Visual acuity at last examination	Classification of retinopathy at last examination
49	F	29	46	6/36	$N_2F_2H_0$	12	6/36	H_2
46	M	31	46	CF	$N_1F_1H_1$	10	CF	H_2
46	F	21	43	<6/18	$N_2F_2H_0$	17	6/60	$N_2F_2H_1$
38	M	8	28	1/60	$N_2F_2H_0$	17	1/60	$N_0F_0H_1$
53	M	26	49	6/9	$N_2F_2H_0$	17	2/60	$N_1F_2H_0$

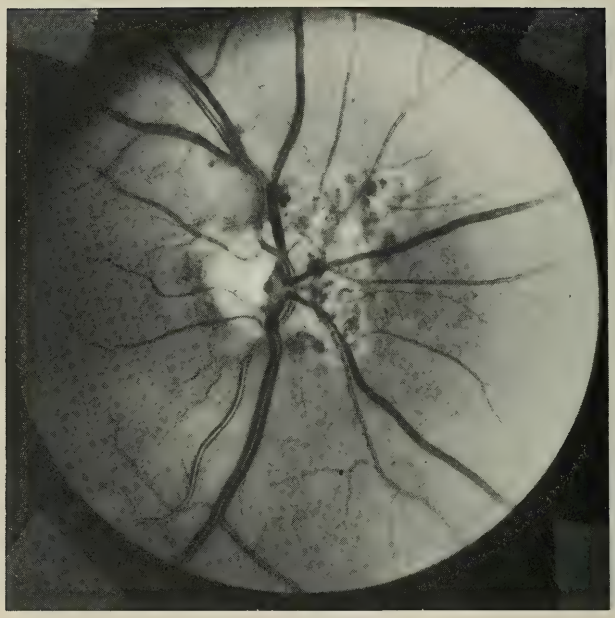

FIGURE 11

FIGURE 12

TABLE 3.—*Average age, 34 years; avcrage duration of diabetes, 20 years*

Age	Sex	Age at diagnosis of diabetes	Age at 1st ocular symptoms	Visual acuity prior to photocoagulation	Classification of retinopathy prior to treatment	Followup period in months	Visual acuity at last examination	Classification of retinopathy at last examination
28	F	4	27	6/6	$N_2F_0H_0$	10	<6/6	$N_0F_0H_0$
28	F	4	27	6/6	$N_2F_0H_0$	8	<6/6	$N_0F_0H_0$
24	M	10	22	6/12	$N_2F_0H_0$	8	HM	H_2
28	F	6	27	6/6	$N_1F_0H_0$	8	6/6	$N_0F_0H_0$
43	M	20	42	6/9	$N_1F_0H_0$	13	6/9	$N_0F_0H_0$
53	M	48	52	6/60	$N_2F_0H_1$	13	6/60	$N_1F_0H_0$
27	M	7	26	6/9	$N_2F_0H_0$	16	6/60	$N_2F_0H_1$
28	M	10	27	6/18	$N_2F_0H_0$	9	6/9	$N_1F_0H_0$
37	M	15	36	6/9	$N_2F_0H_0$	9	6/24	$N_0F_1H_0$
25	F	8	24	6/9	$N_1F_0H_0$	8	6/9	$N_0F_0H_0$
34	M	16	31	6/12	$N_1F_0H_0$	13	<6/6	$N_0F_0H_0$
29	F	16	26	6/12	$N_2F_0H_0$	15	6/18	$N_0F_1H_1$
46	M	8	46	6/6	$N_2F_0H_0$	8	6/6	$N_0F_0H_0$
46	M	8	45	6/12	$N_2F_0H_0$	10	6/6	$N_0F_0H_0$
51	M	23	51	<6/6	$N_1F_0H_0$	17	6/6	$N_0F_0H_0$
41	M	21	41	6/6	$N_2F_0H_0$	9	6/6	$N_0F_0H_0$
25	M	7	24	6/6	$N_2F_0H_0$	21	6/6	$N_0F_0H_0$
26	F	10	25	6/6	$N_1F_0H_0$	8	6/6	$N_0F_0H_0$
32	M	19	31	6/6	$N_1F_0H_0$	14	6/6	$N_0F_0H_0$
32	M	19	32	6/6	$N_2F_0H_0$	8	8/6	$N_0F_0H_0$

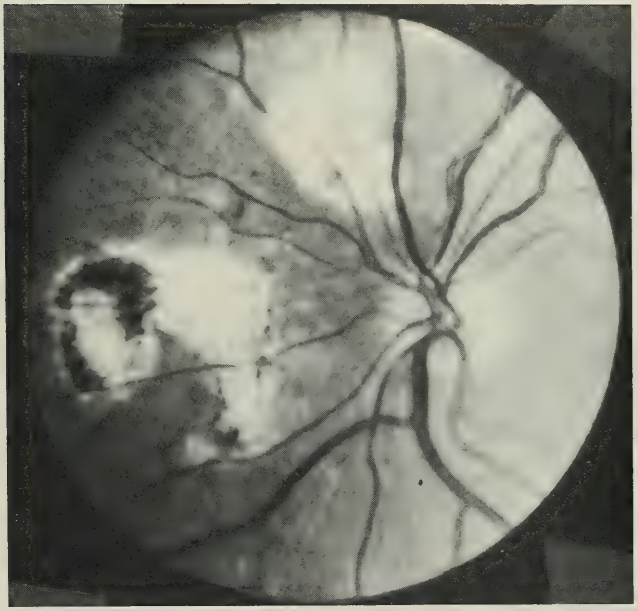

FIGURE 13

FIGURE 14

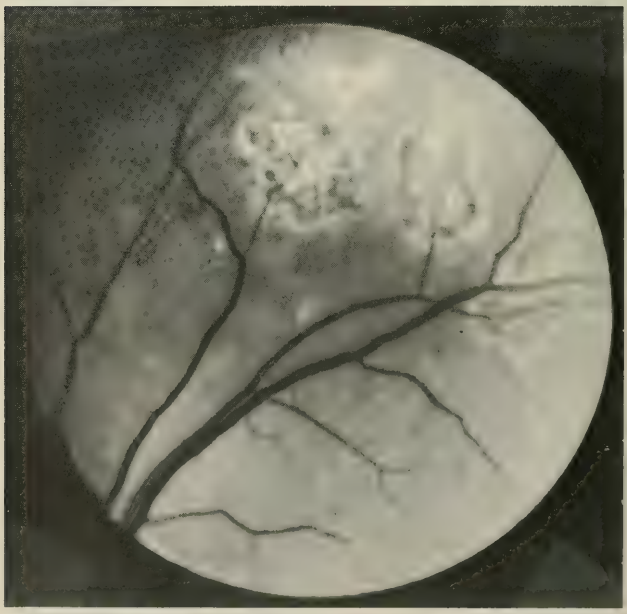

FIGURE 15

TABLE 4.—*Average age, 45 years; average duration of diabetes, 20 years*

Age	Sex	Age at diagnosis of diabetes	Age at 1st ocular symptoms	Visual acuity prior to photocoagulation	Classification of retinopathy prior to treatment	Followup period in months	Visual acuity at last examination	Classification of retinopathy at last examination
41	M	21	41	6/6	$N_2F_1H_0$	15	6/6	$N_0F_1H_0$
35	M	20	25	6/12	$N_2F_1H_0$	9	6/9	$N_0F_1H_0$
35	M	15	26	6/12	$N_2F_1H_0$	13	6/9	$N_0F_1H_0$
58	M	24	54	6/9	$N_2F_2H_0$	9	6/36	$N_1F_2H_1$
57	M	48	57	6/12	$N_1F_1H_0$	8	6/18	$N_0F_1H_0$

COMPLICATIONS

Large retinal, preretinal or vitreous hemorrhage occurred in four of our cases within 2 months after treatment. In two cases gross hemorrhage occurred in both eyes some days after the photocoagulation. This hemorrhage is considered to be due to chance and unrelated to treatment, and the same is considered to be the case in four more patients who developed vitreous hemorrhage more than 2 months after treatment.

Arcuate scotomas were usually present just after the photocoagulation burn. After some time, however, scotomas corresponded only to the fundal scar produced by the photocoagulation, except in two cases where treatment had been too violent.

In three cases, traction in the retina by the chorioretinal scar produced made the morphologically good result a visual failure.

Retinal detachment was not observed in groups 1 to 4, but occurred in group 5.

CONCLUSION

This series showed that neovascularization in the early stages of proliferative diabetic retinopathy can be destroyed successfully by photocoagulation. Later stages and especially those cases with extensive fibrous tissue formation did not react favorably.

It must be stressed, however, that photocoagulation is a palliative treatment which does not cure the disease. New vascular proliferations may occur sooner or later after successful occlusion of neovascularizations. This occurred in this series. The patients must therefore be followed up at intervals and treated again if necessary.

Care should be taken not to produce too heavy burns, which later on may cause traction in the retina or arcuate scotomas, converting these cases into visual failures even though the neovascularization is destroyed.

The average follow-up period this series is about 12 months, making it too short to draw any conclusions as to the long-term prognosis of treatment of proliferative diabetic retinopathy by photocoagulation.

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CHAPTER 40

Photocoagulation as a Treatment of Diabetic Retinopathy

J. WALLACE McMEEL, M.D.
W. A. J. VAN HEUVEN, M.D.

Since the initial reports (*1–4*), light coagulation has been used with increasing frequency to treat diabetic retinopathy. Case selection is most important, as photocoagulation has limited application. Some cases have progressed beyond the point where light coagulation can be effective and others, which are in the indolent nonprogressive phase of retinopathy without threat to central vision, do not benefit from photocoagulation. In this series, the authors report on the treatment of 100 eyes in 94 patients. All were treated with the Zeiss photocoagulator.

To acquire maximum data from these cases on which to base criteria for patient selection and to study the effectiveness of treatment, the patients had several studies in addition to a routine eye examination. The special studies included a large detailed drawing of the fundus, photos of the areas intended for treatment, visual fields, and study of the vitreous cavity and vitreoretinal adhesions by slit lamp and contact lens. To aid the above evaluations an attempt was made to categorize the eyes as to type and severity of retinopathy and vitreous disease. We have used two classification systems for this. The retinopathy has been classified according to Lee et al. (*5*) and the vitreous changes were classified by one of us (W.V.H.) (*6*).

The classification of retinopathy by Lee et al. has been used because it records the degree of angiopathy, vascular and fibrotic proliferation, and gross blood present. All are important factors in the selection of cases for photocoagulation. For this symposium, the stages of the above classification have been fitted into the broader O'Hare Classification.[1] The classification of vitreous by van Heuven has been useful in correlating vitreoretinal adhesions and vitreous shrinkage to the success of photocoagulation. In some eyes the posterior hyaloid face of the vitreous body was intact, with no detachment from the retina or visible vitreoretinal adhesions. A more abnormal finding was a posterior hyaloid face that was totally detached from the retina but without vitreoretinal adhesions. The most abnormal changes were the vitreoretinal adhesions, noted with either shrunken or nonshrunken vitreous gel (*7, 8*).

[1] O'Hare Classification, p. xxi.

Selection of cases for photocoagulation depended on clarity of the ocular media, changes in the vitreous cavity, and type and severity of the retinopathy. Optimally, the eye should have clear media, a vitreous that has not detached or developed vitreoretinal adhesions, and retinal lesions that lie flat, are relatively discrete, located over 20° from the macula, and primarily neovascular with a minimum of fibrotic tissue. Most of our cases did not conform entirely to this ideal, but had most of the desired features.

The data collected from the first 100 eyes treated with photocoagulation reveal the character of the patient population, the type and severity of retinopathy being treated, the technique of treatment, and the results of the therapy. Patients treated fall into four major groups (table I). In those with a mixed retinopathy a decrease in angiopathy would not decrease the chances of becoming blind sufficiently to warrant pituitary ablation. In over 75 percent of the patients the onset of the diabetes occurred before the age of 20 (table II). All but one of the patients with diabetes known less than 10 years prior to treatment had the maturity onset type.

The severity of the retinopathy in the 100 eyes treated was shown by three separate statistics. Over one-half of the eyes had either the N_2 or F_2 (O'Hare Classification) degree of retinopathy and 18 of the 100 were N_2 F_2 indicating that many eyes had rather advanced disease (table III).

Another indication of the severity of retinopathy in the treated eye was the visual acuity of these eyes at the time of treatment. Only 10 of 100 eyes had 20/20, and 13 percent had less than 20/70 (table IV).

TABLE I.—*Indications for photocoagulation of diabetic retinopathy*

Postpituitary ablation—persisting sites of hemorrhage or potential hemorrhage	23
No pituitary ablation because of medical status, age, or patient refusal	15
Mixed retinopathy—decrease in angiopathy	17
Early progressive retinopathy	45
Total	100

TABLE II.—*Relation between patients age at onset of diabetes and duration of diabetes*

Duration of diabetes mellitus	20 years or less	21–30	31–40	41–50	51–60	Over 60	Total
10 years or less	1		1	3	5		10
11 to 20 years	24	11	3	6	1		45
21 to 30 years	16	6	4				26
Over 30 years	11	1	1				13
Total	52	18	9	9	6	0	[1] 94

[1] Juvenile onset—75; maturity onset—19.

TABLE III.—*Severity of proliferative retinopathy (O'Hare Classification—100 eyes)*

	F_0	F_1	F_2	Total
N_0				
N_1	6	35	22	63
N_2	5	14	18	37
Total	11	49	40	100

TABLE IV.—*Vision of the treated eye at time of photocoagulation*

20/20	10	20/200	8
20/25—20/70	77		
20/100	5	Total	100

TABLE V.—*Vision of the fellow eye at the time of photocoagulation*

20/20—20/40	20	Light perception, no light perception, or enucleation	15
20/50—20/100	12		
20/200—20/400	14		
Count fingers or hand movements	27	Total	88

In addition, poor vision in the fellow eye attests to the severity of the disease. Six patients had both eyes treated, but in the 88 untreated fellow eyes the vision was 20/200 or less in 56 (64 percent) (table V).

There were two basic rationales for treatment. The first was to obliterate new vessels, not only to decrease the chance that they would bleed, but also to eliminate them as a site for further proliferation. The second rationale was to decrease the overall metabolic requirements of the retina with the hope that this would result in an amelioration of the neovascularization.

All the patients were treated at the Massachusetts Eye & Ear Infirmary with the Zeiss photocoagulator. The settings of the photocoagulator and the number of applications are noted in table VI. In some instances more than one setting of the photocoagulator was used during a treatment.

The energy levels are higher than used by some, but they were found to be more effective in obliterating nests of neovascularization. Occasionally, photocoagulation was applied to vascularized proliferation in the vitreous cavity. A contact lens (usually +5 or +10) placed on the cornea would usually bring vessels in the vitreous cavity into focus. Our experience with this type of lesion has usually been one of frustration. New vessels adjacent to or extending from the disc were treated in six cases. In the first, a wedge scotoma of 15° arc extended from the blind spot to the periphery. Less intense but more numerous applications averted scotoma formation in the subsequent cases.

Multiple treatments were necessary on 24 eyes (table VII). Although half of those having two treatments were stable after treat-

TABLE VI.—*Intensity and number of photocoagulation applications*

	1st 50 eyes	2d 50 eyes
Green 1	5	
Green 2	28	9
Green 3	22	39
Red 1	1	2
Totals	56	50
Field 1.5°	2	
Field 3°	14	10
Field 4.5°	31	38
Field 6°	8	2
Totals	55	50
Applications:		
50 or less	40	16
51 to 100	10	30
Over 100		4
Totals	50	50

TABLE VII.—*Number of treatments per eye*

1 treatment	76	5 treatments	1
2 treatments	20		
3 treatments	2	Total	100
4 treatments	1		

ment, none of the four cases requiring three or more treatments remained stable. However three of these four still have a vision better than 20/200 in the treated eye despite continued slow progression of the retinopathy.

There were two reasons to evaluate the eyes after treatment. The first was to assess the overall results. The second was to uncover factors in the case selection that significantly affected the success of the procedure.

With the variable course of this disease, clear-cut success or failure was frequently difficult to determine. Therefore, the terms "static" and "progressive" were used instead of "success" or "failure" to evaluate the results of treatment. The term "progressive" was used if there was an increase in the extent or severity of the retinopathy or if new preretinal or vitreous hemorrhage produced a decrease in vision. The term "static" refers to cases that had no demonstrable increase in retinopathy and no decrease in vision due to preretinal or vitreous hemorrhage.

Table VIII summarizes the data that correlate the severity of neovascular and fibrotic proliferation with the course of the retinopathy after photocoagulation. Evaluation of both the vascular and fibrotic aspects of proliferative disease gives a fuller appreciation of the situation than the assessment of either one alone. When the lesions were at the stage of N_1 F_0 or N_1 F_1 there was no progression of

TABLE VIII.—*Correlation of results by photocoagulation with severity of proliferative retinopathy*

	F_0		F_1		F_2	
	Static	Progressive	Static	Progressive	Static	Progressive
N_0						
N_1	5	0	25	10	9	13
N_2	1	2	8	4	6	12

retinopathy in 30 of the 40 eyes (75 percent) in these two categories. If the more advanced stage of either neovascular or fibrotic proliferation was present (N_2 or F_2), only 23 of 52 eyes (44 percent), remained stable. Advanced fibrotic lesions with minimal neovascular lesions (N_1F_2) were treated with less success, only 9 of 22 eyes (41 percent), than advanced neovascular lesions associated with minimal fibrotic lesions (N_2 F_0 and N_2 F_1) in which 9 of 15 (60 percent) remained stable. These results show that the more extensive the lesions of fibrotic proliferation, the less likelihood that photocoagulation would be successful. The above results are statistically significant.[1]

Aside from the status of the proliferative retinopathy, other significant variables concerned the vitreous body. The two facets of importance were the amount of blood in the vitreous cavity and the presence of vitreoretinal adhesions. These are discussed in a separate presentation (W.A.J.V.H.).

Table IX shows how the density of blood in the vitreous gel was graded.

Table X correlates the amount of blood in the vitreous gel, as determined by the slit lamp and contact lens, and the percentage of eyes with retinopathy remaining static after treatment. It shows that significantly greater success was associated with eyes that had an absence or a minimal number of red cells in the vitreous cavity.

In addition to the grading of blood cells in the vitreous cavity, a second vitreous classification was made that concerned itself with the presence or absence of vitreoretinal adhesion or traction. Eyes with no vitreous detachment or vitreoretinal adhesion were classified group I. Group II had vitreoretinal adhesion over areas of retinopathy and

TABLE IX.—*Classification of vitreous blood (as seen with slit lamp and contact lens)*

None	No RBC seen.
Trace	Few enough RBCs to count.
1+	Too many RBCs to count but not diffusely dispersed.
2+	Diffusely dispersed with thousands of RBCs.
3+	RBCs obscuring vitreous detail but retina can still be classified.
4+	Dense RBCs obscuring retinal detail (same as O'Hare H_2).

[1] Determined by a Chi Square test at the .05 level of significance.

TABLE X.—*Relation between blood in vitreous and result after photocoagulation*

[Total number of eyes—81]

Density of blood in vitreous cavity	Static		Progressive		Totals	
	Number	Percent	Number	Percent	Number	Percent
0 to 1+ RBC	21	64	12	36	33	100
2+ to 3+ RBC	22	46	26	54	48	100

NOTE.—4+ RBC not photocoagulated.

usually showed partial vitreous detachment. Group III had total vitreous detachment with no vitreoretinal adhesions.

The eyes of groups I and III, totaling 38 years, had no demonstrable vitreoretinal traction, whereas the 53 eyes in group II did show this traction. Of the 91 eyes thus classified, 78 had a followup of 6 months or greater. Among those with no vitreoretinal traction, groups I and III, 71 percent maintained a static condition after photocoagulation. In contrast, only 36 percent of those with vitreoretinal traction (group II) remained stable (table XI). This difference is statistically significant.[1] Thus the presence of vitreoretinal adhesions and vitreous shrinkage were definitely associated with a worse prognosis.

As even the more subtle vitreoretinal adhesions and signs of shrinkage are significant factors in lowering the prognosis of cases being treated for diabetic retinopathy by photocoagulation, a study of the vitreous by slit lamp and contact lense is necessary to evaluate fully each eye prior to this treatment.

To further polarize our findings, a comparison was made between the cases that had minimal proliferation and vitreoretinal adhesions, N_1 F_1 or N_1 F_0 with no vitreous traction or adhesions, and the cases that had the worst documented change, N_2 F_2 with group II vitreous changes. Only eyes followed 6 months or longer were included. In those with the minimal involvement, 75 percent of the eyes remained static after photocoagulation (nine of 12 cases), and in those with maximal change only 28 percent (four of 14 cases), remained stable.

Other factors, such as duration of diabetes, age of onset of diabetes, sex, age at time of treatment, and type of treatment of the diabetes were studied and found not to be related to the success of treatment.

Of the 40 eyes that had maintained vision and had no progression of retinopathy for a year following treatment, 32 (80 percent) have remained stable through their most recent examinations. In the 90 eyes followed for greater than 6 months, the success rate was 61 percent.

The causes of the 35 failures are noted in table XIII. In some eyes there was more than one factor producing loss of vision.

[1] Determined by a Chi Square test at the .05 level of significance.

From the above data it becomes evident that to have the best chance for success, photocoagulation should be performed when the progressive neovascular proliferative lesions are just appearing. Two things are accomplished by destroying an area of actively progressing neovascularization. First, the nidus for further proliferation is obliterated, and second, development of an overlying vitreoretinal adhesion may be prevented and vitreous traction avoided. However, it must be recognized that photocoagulation may cause vitreoretinal adhesions.

Complications were infrequent, but included loss of peripheral visual field, preretinal or vitreous hemorrhage, and development of preretinal fibrosis. The latter two, which lead to loss of central vision, occurred in less than 2 percent of treatments. Elsewhere, macular burns and the conversion of localized secondary detachments to total rhegmatogenous detachments have been reported.

In summary, photocoagulation was effective treatment for diabetic retinopathy in a limited set of circumstances. It was of no use in treating primarily exudative or avascular fibrotic retinopathy. When there was widespread progressive neovascular retinopathy, particularly if about the optic nerve, pituitary ablation had a better chance of preserving vision.

To select cases for photocoagulation most accurately, the vitreous was studied as well as the retina. The presence of vitreoretinal ad-

TABLE XI.—*Correlation of results by photocoagulation with presence of vitreoretinal traction (status 6 months after photocoagulation)*

Vitreous classification	Static		Progressive	
	Number	Percent	Number	Percent
Groups I and III (no traction)	22	71	9	29
Group II (traction)	17	36	30	64

TABLE XII.—*Results of photocoagulation treatment for diabetic retinopathy*

	Eyes	Percent
Maintenance of vision or arrest of retinopathy	55	61
Progression of retinopathy with loss of vision	35	39
Followup less than 6 months	10	
Total	100	

TABLE XIII.—*Causes of visual loss in treatment failures*

Progressive proliferation	15	Cataract	1
Vitreous hemorrhage	19		
Secondary retinal detachment	2	Total	29
Glaucoma with rubeosis iridis	2		

hesions or moderately advanced fibrotic proliferative retinopathy lessened the chances for successful arrest of diabetic retinopathy by photocoagulation.

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CHAPTER 41

Photocoagulation of Diabetic Retinopathy

CLIVE B. MORTIMER, M.D., F.R.C.S.

INTRODUCTION

This paper will review the treatment of 64 diabetic patients with light coagulation. One hundred and eight eyes have been treated and a total of 160 photocoagulations have been performed. The length of followup varies from 6 years to 6 months. For the majority of patients the followup is between 6 months and 1 year.

Selection of Patients

From the years 1963 to 1966 we regarded pituitary ablation as the first line of treatment for severe diabetic retinopathy and during this period only patients who refused pituitary ablation or were medically unsuitable for it, were treated with photocoagulation. After this time, the encouraging reports from other centers and the inconsistency of our ablation results lead us to consider photocoagulation as an alternative to pituitary ablation. For the last 2 years patients have been assessed medically, and the choice of treatment has been dictated by the patients' wishes, the state of the retinopathy, general medical considerations, and the likelihood of success with one modality or another. The examination of the tabled results will show that within the last year treatment has become more agressive and more severe degrees of retinopathy have been treated.

RESULTS

The detailed results of all treatment according to the O'Hare Classification are in Appendix J.[1] I will here give only a very brief outline as the results themselves are capable of analysis. Using maintenance of vision as the sole criterion of treatment, 62 eyes out of 108 have retained vision at the time of followup. In addition some 15 other eyes have maintained some degree of useful vision, but not within one line of the original preoperative vision. Analysis of the type of retinopathies

[1] See appendix J for raw data on individual patients; O'Hare Classification, p. xxi.

which have maintained vision shows that background retinopathy with vitreous hemorrhage has had the best prognosis. Nevertheless this must be set against the controls which are present within the series. For example in the first group of results, nine eyes retained vision with treatment, but four eyes of comparable preoperative retinopathy also retained vision, and in any treatment of background retinopathy with vitreous hemorrhage the progression of the disease is hard to assess. The second point to emerge from the results is that eyes with neovascularization but without fibrous proliferation into the vitreous, have a much better prognosis than those with fibrous proliferation. The third point that emerges is that the followup shows better results at 6 months to a year than it does at 1 to 2 years, and this is disconcerting and may mean that later some of the presently satisfactory cases will be no longer satisfactory.

Simplified table of results

Classification	Total patients	Retained vision
BH_1	18	17
$N_1F_0H_0$	7	5
$N_1F_0H_1$	25	17
$N_2F_2H_1$	15	1

I do not propose to produce any further simplified analysis of these results as it is to be hoped that they will be considered with all other comparable results and a larger series analysed. The relatively short time of followup and the 15 different classifications of retinopathy does not allow many conclusions to be drawn from the 108 eyes.

The Effects of Photocoagulation

Effect on new vessels

There is little doubt that new vessels in the plane of the retina or closely adjacent to it can be treated satisfactorily. The use of fluorescein intravenously may improve absorption, and this author has used fluorescein consistently for the last 8 or 9 months. Major problems arise in the later stages of the disease where vessels are embedded in leashes of thick fibrous tissue and are elevated away from the pigment layer of the epithelium. I have attempted treatment of these vessels following injection of intravenous fluorescein and used relatively high intensites of heat. I have also experimented with use of filters, attempting to select a filter that would give maximum absorption of

light to fluorescein containing structures. So far filters used have been so dense and allowed a passage of only a small amount of light that this has not been an effective method. Another problem of this type of treatment is to assess any result that is produced. Because the proliferans is separate from the retina, often no visible effect is noted; or sometimes constriction of the vessel is seen, followed by vitreous hemorrhage. I have noted quite a high incidence of mild vitreous hemorrhage occuring at the time of treatment when treating new vessels in the vitreous. Postoperatively the hemorrhage appears to clear relatively quickly and there is, if adequate treatment has been performed, gradual disappearance of the vessels in the leashes of fibrous tissue. It has not been my experience that these vessels can be destroyed completely, because usually they are major vessels coming from the disc and they usually retain some patency.

If the fibrous tissue emerges from the retina at a point away from the disc, the whole area where the vessel comes out into the vitreous may be destroyed. Treatment is effective if carried out in an area two or three disc diameters around the base of the emerging vessel.

Effect on subsequent retinal detachment

I have not noticed that photocoagulation materially effects the development of retinal detachment. I have used photocoagulation in attempts to prevent retinal detachment or to delimit retinal detachment, but I am not certain that treatment is particularly effective in this regard. It is my clinical impression that the majority of diabetics who develop retinal detachment detach at the posterior pole, with gross fibrous tissue coming from the region of the disc usually being the causative fact. It seems unlikely that one would be able, with photocoagulation, to produce a chorioretinal scar which would be as powerful as the dense bands of fibrous tissue which seemed to cause the retinal detachments.

I have not noted a greater instance of retinal detachment following photocoagulation, nor have I noted any definite evidence that it has been prevented.

Effect on vitreous contraction

I have not been able to document any vitreous shrinkage following coagulation of diabetic retinopathy. I have observed consecutive vitreous shrinkage following coagulation of retinal holes, but I believe it to be rare in retinal hole treatment and its instance in diabetics would probably be of the same percentage.

Effect on fibrous proliferation

Effects on fibrous tissue seem most disappointing. The only benefit one may hope to achieve is to shrink the blood vessels contained within the leashes of fibrous tissue. In spontaneous remission and in patients demonstrating remission after treatment, it is noticeable that fibrous tissue changes from pinkish vascular color to a yellowish white. I have seen the change in fibrous tissue color following photocoagulation but I have not noted any regression or disappearance of fibrous tissue as a result of treatment.

Effects on untreated retina

(*a*) Macula degeneration is the most disastrous effect on untreated retina. I have seen macular degeneration following treatment and this would appear to correspond to the incidence of macular degeneration following photocoagulation of upper temporal holes. In my experience this is of the order of a half to 1 percent.

(*b*) In some patients following treatment a spontaneous remission seems to occur. In these patients retinopathy in untreated areas will disappear. I believe this effect is what we are hoping to achieve with photocoagulation and represents the burnt out stage of the disease. It is interesting that patients with large chorioretinal scars from other causes often do not develop severe retinopathy and the creation of a large chorioretinal area of destruction is sometimes associated with regression of the retinopathy in all areas.

(*c*) Effects on untreated retina do not appear to be regional and there is no evidence that benefit is seen immediately adjacent to sites of treatment. Benefits in untreated areas seem to be either related to general regression or arbitrary.

COMPLICATIONS

(1) Vitreous hemorrhage.
(2) Macular degeneration.
(3) Heat optic neuritis.
(4) Retinal detachment.
(5) Secondary glaucoma.

The principal complication of treatment is vitreous hemorrhage. This may be either as a consequence of the treatment or failure to prevent further hemorrhage. I have had the interesting experience in an untreated patient of seeing a vitreous hemorrhage occur in the course of a routine examination. The hemorrhage occurred from a major ves-

sel within one and a half disc diameters of the disc at an arteriovenous crossing, at a site that was ophthalmoscopically normal. Unfortunately, I had not injected intravenous fluorescein into this patient prior to the examination and was not able to know if there had been a fluorescein leakage at this site prior to the visible vitreous hemorrhage. The occurrence of vitreous hemorrhage from apparently normal vessels is one of the difficulties of treatment and one of the reasons why complications are so hard to assess. Hopefully the injection of intravenous fluorescein may enable us to detect sites of potential vitreous hemorrhage prior to gross leaking. I think intravenous fluorescein is a most important diagnostic tool and should be used routinely in the preoperative assessment. Clinically it is my impression that those patients who show early pooling of fluorescein around the disc shortly after fluorescein injection are leaking from their major vessels and are bad candidates with a poor prognosis. I have noted a number of patients who have run a relatively benign course for a number of years and then enter a period of activity in which new-vessel formation and retinitis proliferans formation are rapid. Fluorescein angiography in these patients demonstrates large vessel leakage and multiple new vessel formation. These patients may progress within a period of 3 months from 20/20 to less than 20/200. Treatment started coincidentally with the onset of this acute phase is bound to be disappointing. Nevertheless, the onset of this phase, which is usually diagnosed by the change in the fluorescein pattern, is a definite indication for starting treatment. I do not believe that the rapid progression seen in these patients is the consequence of treatment as I have observed it frequently in untreated patients.

Heat optic neuritis is a complication which I have observed since attempting to treat new-vessel formation at and near the disc. In severe cases the patient's vision may be reduced to inaccurate light perception on the day following treatment. Usually it recovers within a week without medication, but some of these patients may be left with a persistent sector defect, corresponding to damaged nerve bundles at the disc. If bleeding is occurring from large vessels at and near the disc, I believe that the risk of optic neuritis is worth taking in an attempt to close the dangerous vessels.

DETAILS OF TREATMENT

All patients have been treated with a Zeiss West German photocoagulator, following injection of intravenous fluorescein. The fundus is visualized, and areas which have previously been determined by fundus photography and examination are treated. The setting is usu-

ally the minimum setting which will produce a burn. Commonly green No. 1, is used without diaphragm and with a setting of either 4.5 or 6 on the aperture. Smaller apertures are used when the macula area is approached. Duration of burn is one-half to 1 second, and the end point used is the appearance of an adequate burn. Only one application is given to any one area at a time. If the area is mostly white fibrous tissue and shows no response to the treatment, no further treatment is given at that session. Treatment is aimed particularly at areas of new-vessel formation, areas at the base of retinitis proliferans, and large aneurysmal dilatations. The disc is not spared and the regions immediately adjcent to it are treated if they contain new vessels or retinitis proliferans. The disc itself is also treated but an effort is made to retain the patency of the large major vessels. It has been my clinical impression that in fact these vessels are very difficult to occlude with normal intensities of treatment. The papillomacular bundle is always spared. Treatments are carried out often above or immediately below the upper and lower temporal veins, but seldom within the region between the disc and the macula. I have noted visual improvment from treatment in the vicinity of the macula when areas of hemorrhage and aneurysm formation have been treated adjacent to the macula. In these patients macular exudate may show regression over a period of a month to 2 months following treatment. I have not found any constancy in this and do not know whether the improvement is specifically the result of the treatment or spontaneous improvement.

I have not found it practical to treat all areas of retinopathy or all hemorrhages or aneurysms as has been suggested by some authors. Where there is widespread background retinopathy, I think it important to treat either those which leak fluorescein after intravenous fluorescein injection, or to treat those associated with new-vessel formation or preretinal fibrosis. If the disease is very widespread, I attempt to treat all major areas of hemorrhage while trying to maintain the patency of major vessels. If there is an area of extensive local hemorrhage with new-vessel formation I will attempt to obliterate the whole area of the retina that contains it. I do not make any attempt to treat retina containing exudate and normally I do not treat background retinopathy unless vitreous hemorrhage has occured.

Frequency of treatment depends on the progress from one treatment to another. I attempt to follow my patients on a 6-week to 2-month basis. If the first treatment has failed to occlude new vessels or shrink vessels in retinitis proliferans, treatments to the same areas are repeated. If following the first treatment, there has been no further vitreous hemorrhage and the retinopathy appears static, then no fur-

ther treatment is carried out, but photography is repeated and the patient continued in the followup group. As long as patent vessels remain in areas of retinitis proliferans and the patient is still bleeding, I will repeat treatments. I believe intravenous fluorescein photography is a most useful agent in followup and often enables one to see which retinas need treatment.

SUMMARY

Sixty-four patients from the Toronto General Hospital treated with photocoagulation have been reviewed. The results of 108 eyes are detailed in Appendix J and some simplified conclusions have been drawn. The effects of photocoagulation based on this experience have been detailed and the ideal selection of patients has been considered.

Role of Photocoagulation in the Treatment of Proliferative Diabetic Retinopathy: Continuation and Followup Studies [1] *(359 Eyes of 283 Patients)*

EDWARD OKUN, M.D.
GLEN PAUL JOHNSTON, M.D.

INTRODUCTION

Photocoagulation has been shown to be an effective method of eliminating areas of neovascularization in the diabetic eye (*1*, *2*, *3*). Preliminary studies have indicated that properly applied photocoagulation lesions slow down the rate of progression of proliferative diabetic retinopathy (*4*). Since the rate of morphological deterioration is usually more rapid than the rate of visual decline, a morphological classification has been helpful in the evaluation of therapy (*1*, *4*).

In the present report we shall endeavor to convert our system of classification to that agreed upon at the O'Hare meeting.[2] Although this reclassification is less detailed than that which we have used, it will, nevertheless, allow for gross comparative observations concerning both the types of cases being treated and the effects of therapy.

METHOD

The vast majority of patients were treated with the Zeiss photocoagulator (after Meyer-Schwickerath). Some patients were treated with the Zeiss-Jena indirect photocoagulator, and a small number with the Optics Technology laser. The latter two instruments were used more for supplementary therapy than for initial therapy, and are not being independently evaluated in this report.

Initial therapy depended upon the status of the vitreous. In cases of vitreous hemorrhage, only the site or sites of origin of the hemorrhage were coagulated. In eyes with clear media, areas of neovascular-

[1] See appendix K for raw data on individual patients.

[2] O'Hare Classification, p. xxi.

From the Department of Ophthalmology and the Oscar Johnson Institute, Washington University School of Medicine, St. Louis, Mo. 63110.

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ization and retinal hemorrhagic activity were directly coagulated, all four quadrants at one sitting. After the media had cleared, this same therapy was also applied to eyes which previously had been treated only at the site of origin of vitreous hemorrhage. Care was taken to keep lesions out of the macular zone, and to avoid direct hits on large veins. Areas of neovascularization originating from large veins were eliminated by straddling the veins (fig. 1a–c). Arteries could be directly coagulated without ill effect. One hundred to 300 lesions were delivered at one sitting in most cases. The 4.5° aperture was used routinely, and the intensity setting varied with the degree of pigmentation in the eye. The desired lesion was one which whitened the entire thickness of retina, in less than one-half second, with the least amount of energy.

RESULTS

Since February, 1960, 359 eyes of 283 patients have received photocoagulation treatment for their proliferative diabetic retinopathy (PDR). Appendix K lists and classifies the eyes of these patients. Tables I and II show the rate of morphological progression for eyes which initially exhibited various stages of involvement, and were fol-

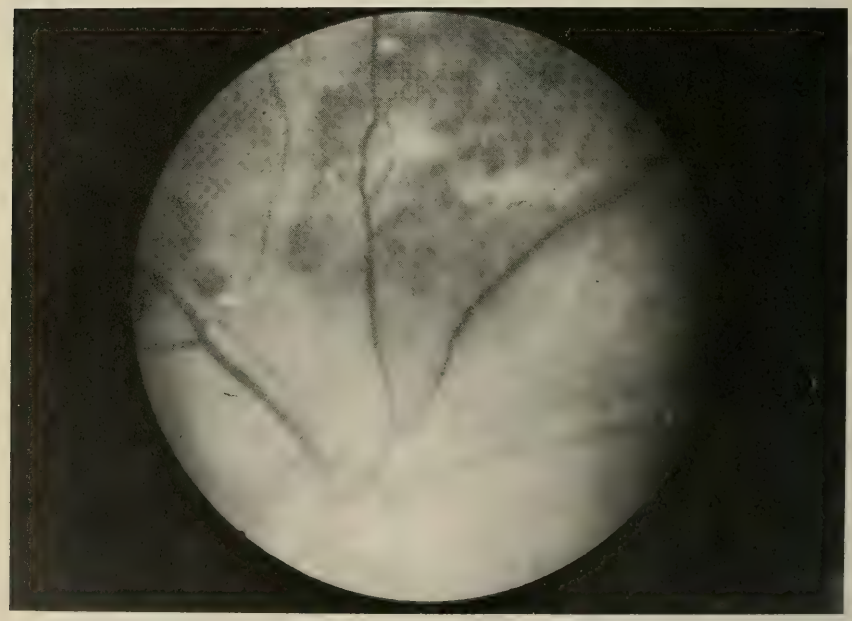

FIGURE 1*a*.—*Preretinal neovascularization originating from superior vein.*

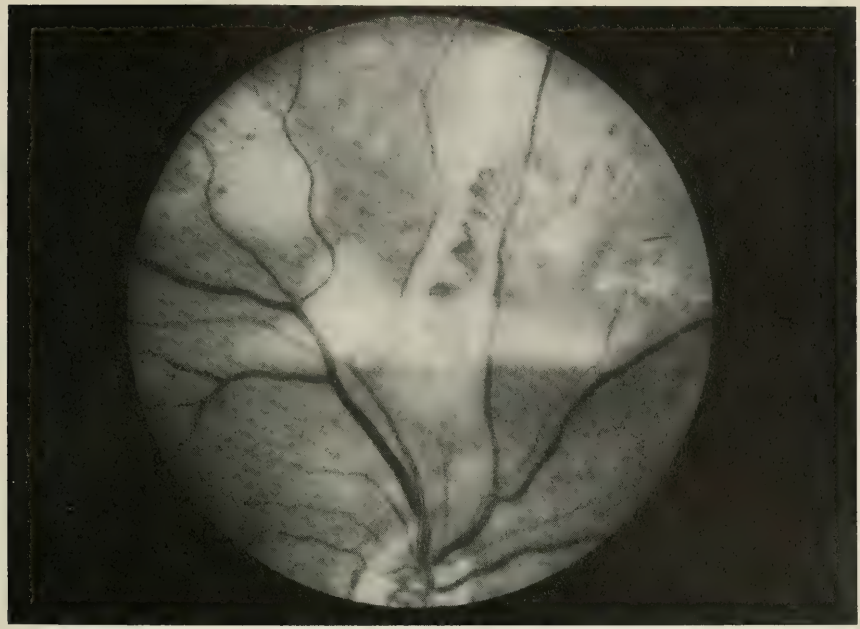

FIGURE 1*b*.—*Photograph of same area 1 day after photocoagulation. (Horizontal light streak across center of field is light reflex).*

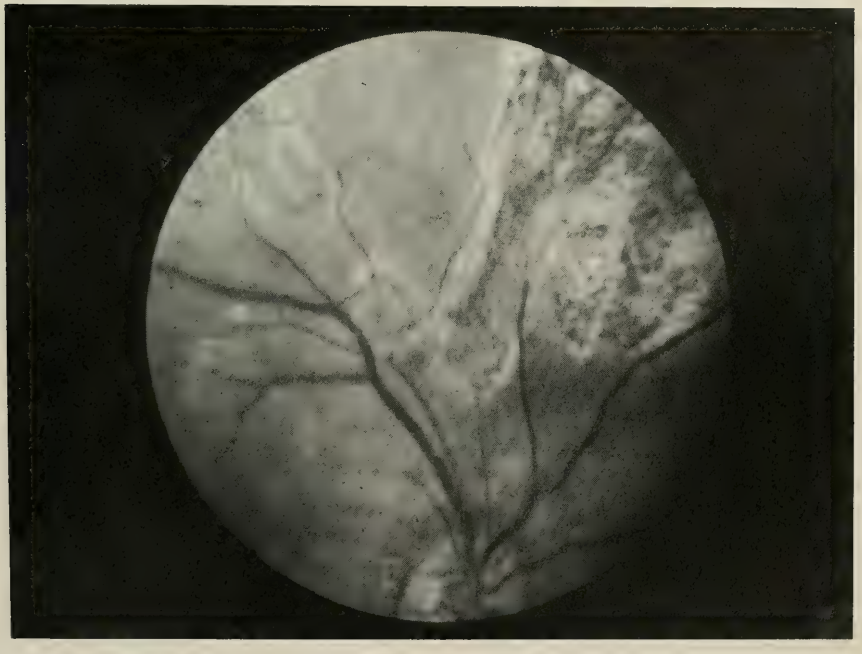

FIGURE 1*c*.—*Same zone 2 weeks later. Neovascularization has been eliminated, and replaced by chorioretinal scar.*

TABLE I.—*Progression of PDR in treated eyes followed longer than 6 months*[1]

Classification at time of Rx		Number of eyes	Number stabilized	Percent stabilized
F_0	N_1	40	29	75
	N_2	100	71	71
F_1	N_1	2	2	—
	N_2	75	44	59
F_2	N_1	0	—	—
	N_2	37	20	54
Totals		254	166	65

[1] Followed 6 to 72 months.

NOTE.—Average followup—28 months, 43 patients now deceased.

lowed for a minimum of 6 months. From these tables it is apparent that the eyes which were less severely effected from the start had the better prognosis. Seventy-five percent of 40 eyes with N_1F_0 have remained relatively stable compared to only 54 percent of 37 eyes with N_2F_2. Between these two extremes, the prognosis gradually deteriorates from N_1 to N_2, and from F_0 to F_2.

Visual deterioration follows a similar pattern (table III). The more severely affected eyes show a more rapid visual loss.

Tables IV and V show the followup of a group of patients who initially had symmetrical involvement, and in whom only one eye was treated. In this group of 52 eyes, the treated eye, when compared to the nontreated eye, showed less progression in 23 patients, while the untreated eyes showed less progression in only one. The visual acuity

TABLE II.—*Progression of PDR in treated eyes followed longer than 6 months*[1]

Classification at time of Rx		Number of eyes	Number stabilized	Percent stabilized
N_1	F_0	40	29	75
	F_1	2	2	—
	F_2	0	—	—
N_2	F_0	100	71	71
	F_1	75	44	59
	F_2	37	20	54
Totals		254	166	65
Age groups	<25 yrs.	12	7	58
	25–50 yrs.	101	67	66
	50+ yrs.	141	92	65

[1] Followed 6 to 72 months.

NOTE.—Average followup—28 months, 43 patients now deceased.

TABLE III.—*Change of visual acuity in treated eyes followed longer than 6 months* [1]

		Before Rx			After Rx		
		10/400 or less	20/400–20/100	20/70 or better	10/400 or less	20/400–20/100	20/70 or better
N_1	F_0	3	7	30	4	8	28
	F_1		1	1		1	1
	F_2						
N_2	F_0	12	23	65	29	26	45
	F_1	7	23	45	36	14	27
	F_2	16	7	14	19	10	8

[1] Followed 6 to 72 months.

NOTE.—Average followup—28 months, 43 patients now deceased.

TABLE IV.—*Uniocularly treated symmetrical PDR, 52 patients* [1]

	Anatomical classification	Visual acuity
Better in treated eye	23	19
Better in untreated eye	1	5
Same in both eyes	28	28

[1] Followed 5 to 52 months.
Average followup—29 months.

was better in 19 of the treated eyes, and in only five of the untreated eyes. Seven of the initially untreated eyes have received photocoagulation because of rapid progression of the proliferative processes, threatening complete destruction of the eye. Eleven of the untreated eyes progressed to count fingers or worse visual acuity secondary to irreversible vitreoretinal changes. Seven of the treated eyes showed visual deterioration to a similar extent, but primarily due to rubeosis and secondary glaucoma (four eyes). One eye developed an unex-

TABLE V.—*Uniocularly treated symmetrical series progression of PDR*

[Average followup—29 months]

Classification at time of treatment		Number of of eyes	Treated eyes stabilized	Percent stabilized	Nontreated eyes stabilized	Percent stabilized
N_1	F_0	20	17	85	13	65
	F_1	1	1		0	
	F_2					
N_2	F_0	20	16	80	5	25
	F_1	6	2	33	1	17
	F_2	5	3	60	1	20
Totals		52	39		20	

plained optic atrophy, and two eyes lost vision secondary to vitreous hemorrhage.

The treated eyes not infrequently showed a marked regression of the vasculopathy. The veins appeared less distended and the arterioles slightly more attenuated. The retina itself appeared less edematous, its color improving from a yellowish to greenish background hue to a more healthy red appearance. In some instances, partial optic atrophy had become evident, and this has been accompanied by disappearance of the rete mirabile of the disc.

In certain selected cases, eyes with macular edema and exudation have had photocoagulation treatment to areas of capillary leakage surrounding the macula with marked improvement of macular appearance and function.

Of special interest were the following facts:

(1) Forty-three patients in this series of 283 patients treated with photocoagulation are now deceased.

(2) Thirty-one of the 359 eyes treated have gone on to retinal detachment.

(3) Sixty-six percent of those with H_0, when first seen, were stabilized with treatment. Forty-one percent of those with H_1, when first seen, were stabilized with treatment.

Complications encountered with photocoagulation therapy of proliferative diabetic retinopathy (PDR) have been discussed in a previous communication.

DISCUSSION

Our studies indicate that photocoagulation can be useful in prolonging the life of an eye affected by proliferative diabetic retinopathy. There is probably more than one mechanism at work. Since vitreous hemorrhage plays a very important role in reducing visual function and increasing the rate of progression, the elimination of possible sources of this hemorrhagic activity is the prime rationale of our therapy. Our aim, therefore, is to clear the fundus of neovascularization. This is best accomplished by direct coagulation of these abnormal vessels whether they be fan-shaped, mulberrylike, or just irregular preretinal capillary networks (figs. 2a–c, and 3a–b). In cases of vitreous hemorrhage, the site of origin can frequently be detected and directly treated, (fig. 4a–b).

In addition to the direct effects of treatment on neovascular tissue, we have become impressed that widespread therapy of the entire fundus, concentrating on zones of hemorrhagic and exudative ac-

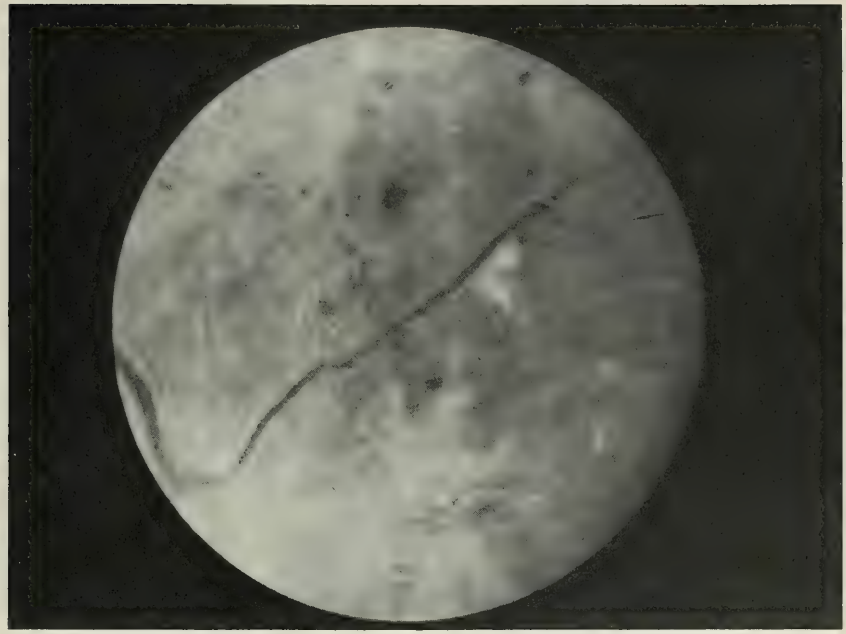

FIGURE 2*a*.—*Neovascularization originating from superior vein.*

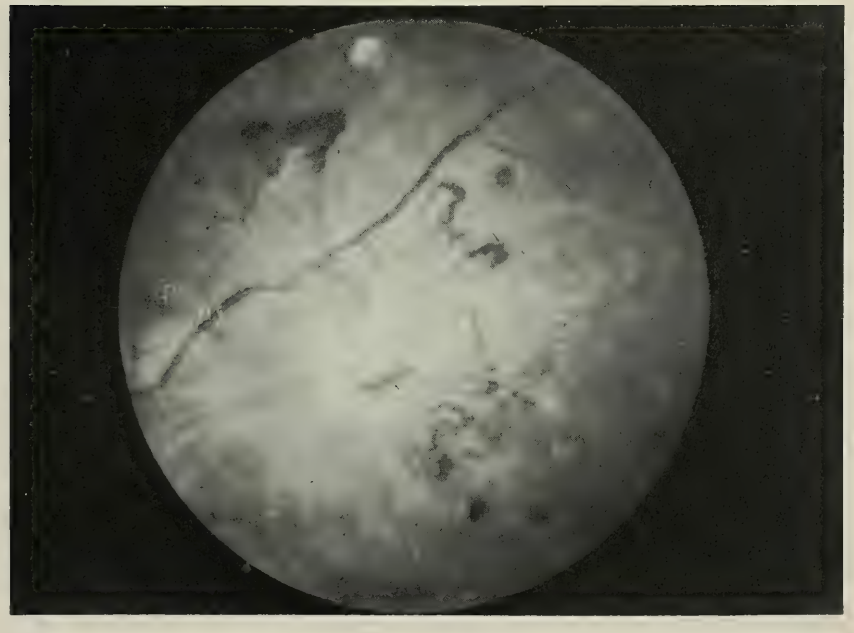

FIGURE 2*b*.—*Same zone 1 year later.*

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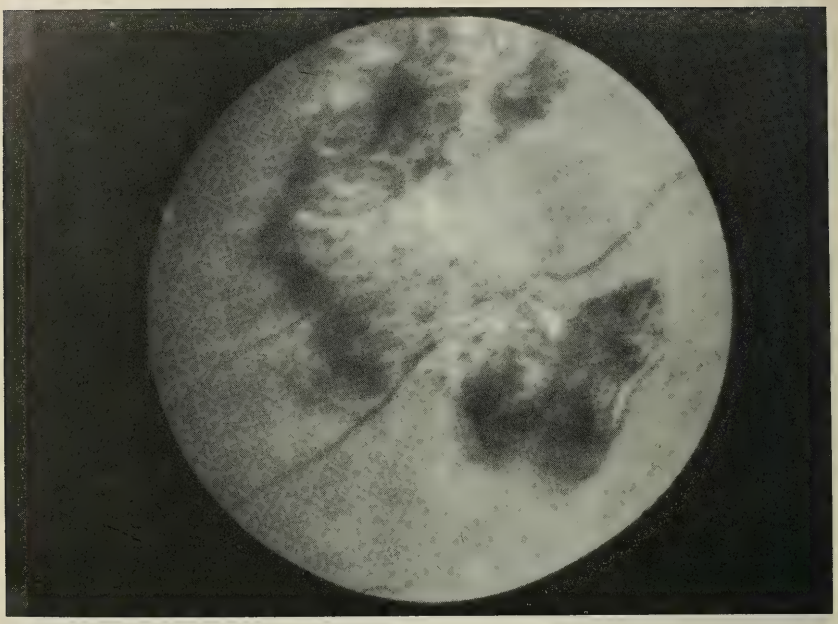

FIGURE 2c.—*Same zone 1 month after photocoagulation. Arcades of neovascularization have been eliminated, and replaced by a chorioretinal scar.*

tivity, has been followed by a decrease in the rate of growth of new vessels. These eyes begin to behave like eyes which we have observed to be protected against proliferative diabetic retinopathy (PDR). Eyes with optic atrophy, advanced glaucoma, myopia and chorioretinal degeneration have been noted to be spared severe proliferative changes, while the normal fellow eyes have shown advanced changes. Diabetic eyes with spontaneous involutional changes show marked attenuation of retinal vessels and partial optic atrophy, probably secondary to hemosiderosis. These protected eyes have in common, a decrease in retinal substance and less demand for vascular supply. Eliminating zones with borderline nutritional supply may eliminate a vasoproliferation-inducing substance, as well as decrease the amount of retina which must be nourished. We have documented the regression of new formed vessels at some distance from zones of photocoagulation, even though the vessels were not directly affected (fig. 5a–c).

It is apparent from this study that the most effective time for photocoagulation is during the early stages of the proliferative process, before very large areas of the fundus have been affected, and before vitreous retraction has occurred. It therefore, becomes essential that we learn to prognosticate which cases are likely to go on to stages N_2 and F_2. Serial fundus photographs help to determine progression and

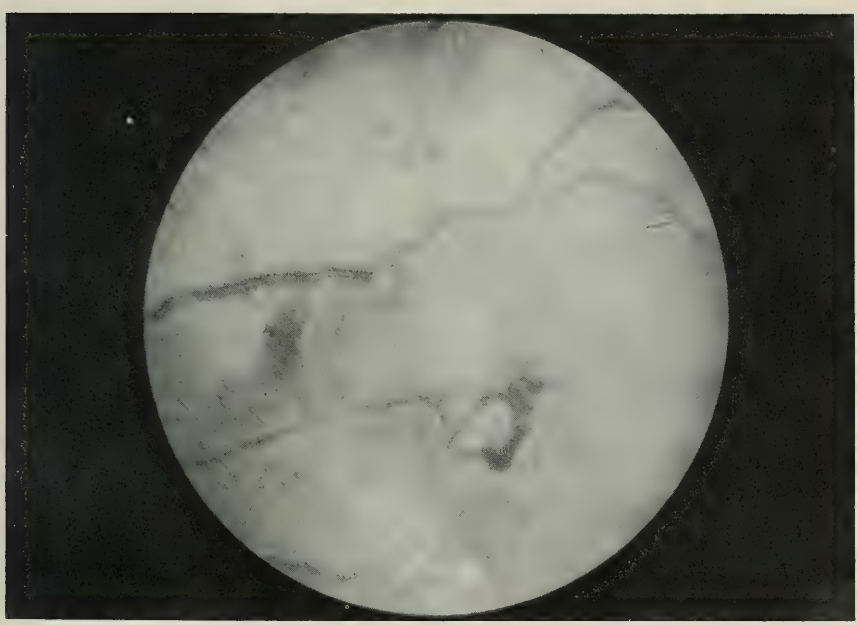

FIGURE 3a.—*Mulberry-like lesions plus other areas of surface neovascularization before photocoagulation.*

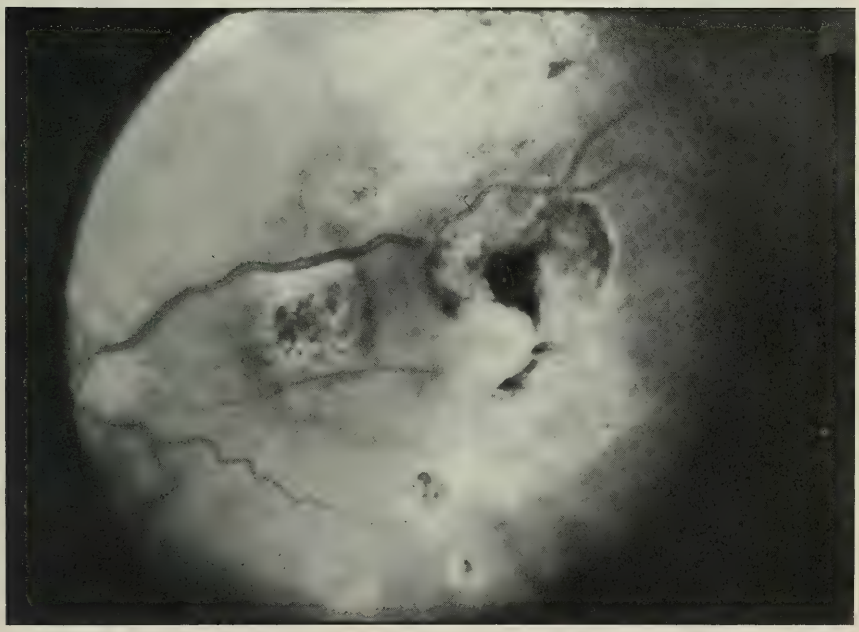

FIGURE 3b.—*Same field 6 months after photocoagulation. Neovascularization replaced by chorioretinal scar.*

FIGURE 4a.—*Site of origin of vitreous hemorrhage.*

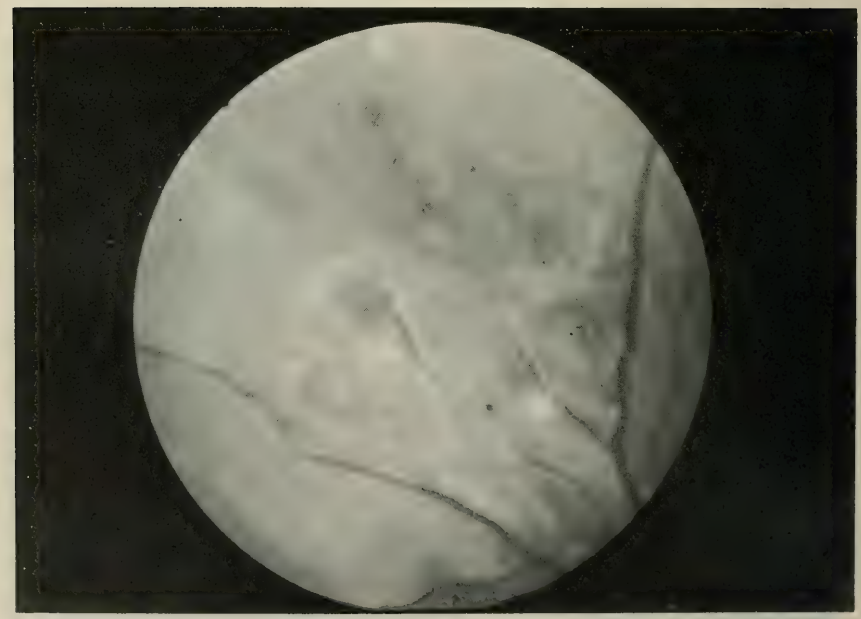

FIGURE 4b.—*Photocoagulation scar 1 month following treatment of site of origin.*

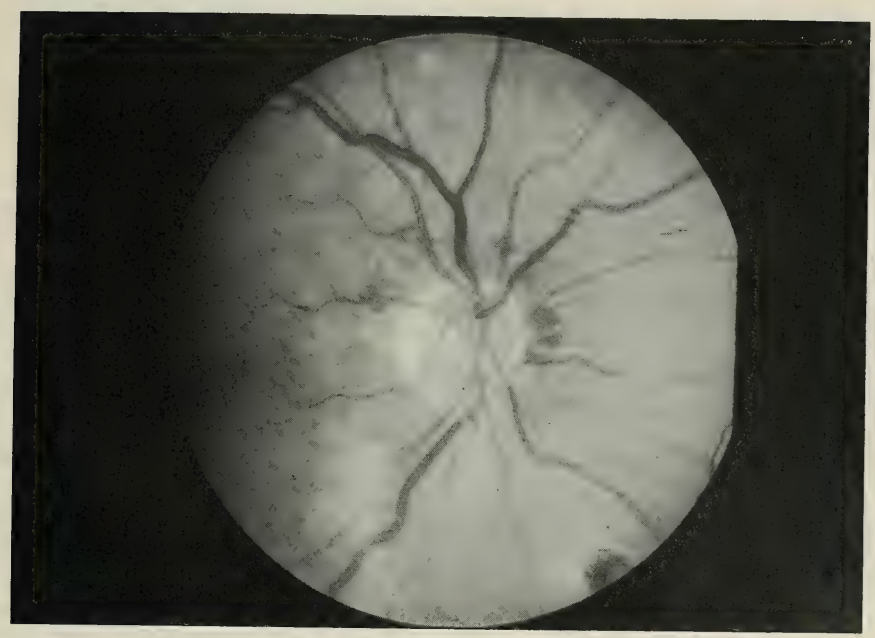

FIGURE 5a.—*Papillary and peripapillary neovascularization.*

FIGURE 5b.—*Same area 2 years after photocoagulation therapy of peripheral neovascularization. Note early optic atrophy and decrease in venous distension.*

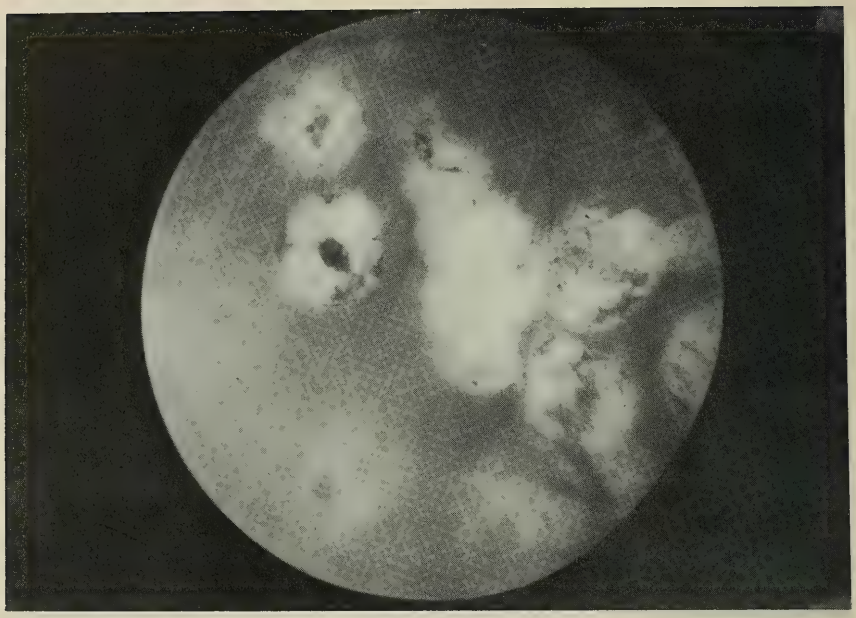

FIGURE 5c.—*Same eye—area of photocoagulation treatment inferior temporal quadrant.*

also allow us to reexamine the appearance of the fundus prior to progressive changes.

Only after we learn to prognosticate in each individual eye will we be able to pick out the proper cases for photocoagulation. Thus far, we have learned that eyes with numerous areas of occluded small vessels, engorged tortuous veins, and small zones of neovascularization are destined for trouble. Areas of venous reduplication and attempts at development of collateral blood flow are frequently seen in eyes with rapidly advancing neovascularization. Areas of early neovascularization can be eliminated by direct treatment, while widespread photocoagulation into the zones with borderline vascular supply seems to be a method of avoiding further growth of new vessels.

SUMMARY

A followup study of 359 eyes of 283 patients with proliferative diabetic retinopathy (PDR) who have been treated by photocoagulation indicates that the therapy is of greatest value when applied relatively early in the course of the disease process. A followup study of 52 patients who had uniocular treatment for symmetrical disease

indicated that photocoagulation is effective in slowing the rate of progression of the disease process.

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CHAPTER 43

Light Coagulation as an Adjunct to Cryohypophysectomy [1]

NATHAN H. ROTH, M.D.
ROBERT W. RAND, M.D., Ph.D.

Since diabetic retinopathy has become one of the leading causes of new blindness in the United States (*1*), the concern of the ophthalmologist for management of these patients continues to increase. The recent interest in light coagulation as a form of treatment (*2–9*) has prompted us to utilize this therapy in selected cases, to attempt an evaluation of its effectiveness, and to establish standards for its use. At present we tend to view the use of cryohypophysectomy in the light of our past experience and to use it in conjunction with light coagulation.

Cryohypophysectomy has been used effectively at the UCLA School of Medicine for 3 years to treat documented cases of progressive retinopathy (*10*, *11*). We continue to treat selected patients who fulfill the systemic as well as the ophthalmological requirements: one clinically healthy macula and evidence of progression of the retinopathy. Progression is documented by comparative retinal drawings and fundus photography. The selection of patients for this procedure is made by a multidisciplinary group of physicians in the Neuroendocrine Clinic at the UCLA School of Medicine. Best results are obtained when ophthamological evaluation is based on a certain degree of previous experience. Progression of the disease manifests itself in the form of vasoproliferation and in repeated retinal and vitreous hemorrhages, which take longer to clear each time and show continued visual loss. We have chosen an arbitrary visual acuity of no worse than 20/60 to 28/80 in the better seeing eye as a cutoff point for this procedure.

We will report our approach to the use of this therapy and our thoughts concerning its place in the treatment of diabetic retinopathy. We have used photocoagulation to treat patients with areas of vasoproliferation and retinal hemorrhage before and after cryohypophysectomy. We also use it in patients with progressive retinopathy who fail to meet all the requisites for pituitary surgery. These usually include patients over age 50 and those with severe kidney and vascular

[1] See appendix L for raw data on individual patients.

From the Departments of Ophthalmology (Jules Stein Eye Institute) and Surgery (Division of Neurosurgery), UCLA School of Medicine, Los Angeles, Calif.

disease. It has also been used on patients being followed as potential candidates for cryohypophysectomy, where the retinopathy is considered to be at an early stage.

PREPARATION OF PATIENT

When possible, the patients for photocoagulation are handled on an outpatient basis under the supervision of an internist. Usually the insulin dosage is reduced while the patient is allowed to continue his regular diet on the day of surgery. If the patient is hospitalized, it is usually for a 24-hour period. For at least 1 week after the treatment, however, he is placed on restricted activity. When possible, only one eye is treated during one session.

TREATMENT

Confluent and overlapping lesions are avoided in an attempt to minimize significant loss of the visual field. Primarily, discrete areas of vasoproliferation, retinal bleeding, and exudates are treated. Where indicated, lesions are made up to one-half disc diameter from the macula. The superior, temporal, and inferior edges of the macula are considered for treatment. Where most of the pathology centers in the disc and macular areas, an attempt is made to treat near the macula, especially when macular vision has been seriously affected in one eye, and when only the optic nerve head and macular areas are involved by the disease. An attempt is made to avoid large vessels for fear of causing additional hemorrhage. If hemorrhage occurs, immediate additional photocoagulation is utilized to halt it. Injection of fluorescein during the procedure helps to outline bleeding areas and occasionally serves to help photocoagulate vessels extending into the vitreous. Should the angiopathy encompass too great an area of the retina, or if retinal bleeding proves too extensive or clouds the media to the extent that photocoagulation cannot be considered, cryohypophysectomy would be our treatment of choice.

Cryohypophysectomy

Patients being considered for cryohypophysectomy have usually had an initial evaluation by endocrinologists, neurologists, the neurosurgeon, and the psychiatrist, during visits to the neuroendocrine clinic.

When a tentative decision is made for surgery, the patient is admitted to the hospital for a final medical evaluation. Surgery is performed under local anesthesia and a freezing probe is directed to the pituitary gland transsphenoidally by a stereotaxic device (*10*). By seeing the patient at frequent intervals new areas of vasoproliferation, should they occur, can be treated by photocoagulation. Large bleeding sources frequently clear following cryohypophysectomy, and remaining or new small areas of vasoproliferation or bleeding will respond to additional light coagulation.

RESULTS (Appendix L)

Thirty-two patients have undergone photocoagulation for diabetic retinopathy. Originally these patients were referred to us for evaluation as candidates for cryohypophysectomy. Our followup ranges from 2 weeks to 37 months. Of the 32 patients, we have a total of 46 eyes undergoing treatment one or more times. Seven eyes have been treated two times (patients 5, 14, 15, 17, 24, 26, 32) and one eye has been treated three times (patient 11). Our average length of followup is 9.7 months. All patients thus far have been white. Our group comprised 22 men and 10 women with 23 right eyes and 23 left eyes treated. The following age distribution is noted (table I) : average age of 32 patients, 47.7 years; average age of 25 of our patients at the time of diagnosis of diabetes mellitus, 27.9 years; average age of 28 patients at the time of first subjective eye symptoms, 44.7 years; and average age at the start of treatment of our group, 46.7 years. Of the 46 eyes treated (table II), 32 or 69.6 percent have shown improvement or retention of visual acuity measured at the start of treatment. Fourteen eyes or 30.4 percent have shown deterioration of visual acuity.

An attempt to evaluate visual acuity as a criterion for treatment

TABLE I.—*Age distribution in patients undergoing photocoagulation*

	Years
Average age (32 patients)	47.7
Average age at diagnosis of diabetes (25 patients)	27.9
Age at time of 1st eye symptoms	44.7
Age at start of photocoagulation	46.7

Table II.—*Results of photocoagulation (46 eyes)*

Outcome	Number of eyes	Percent
Improved or stable	32	69.6
Progression of disease	14	30.4

revealed the following (table III): among the patients showing retention or improvement in vision following photocoagulation, 56.3 percent of the eyes treated had a visual acuity of 20/50 or better at the beginning of treatment; 43.8 percent had a visual acuity of 20/60 or less; and 18.8 percent of the eyes had visual acuity of 20/100 or less. Among the patients who, despite treatment, showed deterioration of vision, 28.6 percent of 14 eyes had a visual acuity of 20/50 or better, 78.6 percent had a visual acuity of 20/60 or less, while 42.9 percent showed a visual acuity of 20/100 or less at the beginning of treatment (table IV).

The visual retention index in 46 eyes (table V) is equal to 0.804. Two patients (12 and 31) have undergone cryohypophysectomy since their initial photocoagulation. This was considered necessary since each of these patients had only one usable eye and additional retinal hemorrhages were occurring despite photocoagulation. However, at the time of cryohypophysectomy, these patients had the same vision as before photocoagulation. Patient 31, since undergoing cryohypophysectomy, developed an inappropriate antidiuretic hormone syndrome with recurrent vitreous hemorrhages and subsequent deterioration of vision. There has been one death in our series (patient 25 died of coronary artery disease approximately 1 year after the beginning of his photocoagulation). Several of our patients showed poor control of their systemic diabetes. Patient 1 is such an example. Also, patient 24 proved to be a very brittle and poorly controlled diabetic, as well as mentally unstable. This patient is currently being maintained in a state mental institution and has developed recurring vitreous hemorrhages and secondary glaucoma. Patients 17, 19, and 22 have been on PAS therapy at various times during their treatment.

TABLE III.—*Visual acuity of patients showing retention or improvement in vision following photocoagulation (32 eyes)*

Visual acuity at start of photocoagulation	Number of eyes	Percent
20/50 or better	18	56.3
20/60 or less	14	43.8
20/100 or less	6	18.8

TABLE IV.—*Visual acuity of patients showing progression of disease despite photocoagulation (14 eyes)*

Visual acuity at start of photocoagulation	Number of eyes	Percent
20/50 or better	4	28.6
20/60 or less	11	78.6
20/100 or less	6	42.9

TABLE V.—*Visual retention index (46 eyes)*

$$\frac{\text{Average retention V.A. (mos.)}}{\text{Average followup (mos.)}} = \frac{7.8}{9.7} = .804$$

TABLE VI.—*O'Hare Classification*[1]

INCIDENCE OF PREOPERATIVE FINDINGS IN PHOTOCOAGULATION PATIENTS

	B	N_1	N_2	F_0	F_1	F_2	H_0	H_1	H_2
Occurrence in number of eyes		5	39	11	15	17	19	23	1
Percentage of total		11.4	88.0	25.6	34.9	39.5	44.2	53.5	2.3

INCIDENCE OF POSTOPERATIVE FINDINGS IN PHOTOCOAGULATION PATIENTS

Occurrence in number of eyes	2	19	23	16	11	16	30	13	
Percentage of total	4.5	43.2	52.3	37.2	25.5	37.2	69.8	30.2	

[1] See O'Hare Classification, p. xxi.

DISCUSSION

Our group of patients undergoing photocoagulation show an older age distribution than those selected for cryohypophysectomy. This is understandable since we have a cutoff point of approximately 50 years of age when considering a patient for cryohypophysectomy. Several of the older patients of this series were denied pituitary surgery for this reason. Several of these patients also failed to meet the systemic criteria for cryohypophysectomy (patients 1, 7, 13, 15, and 24). Frequently patients with early retinopathy were considered too early for cryohypophysectomy. All of the patients however, demonstrated elements of proliferative retinopathy. Because of the relative simplicity of photocoagulation and the small number of complications attached to the procedure, we tend to recommend it readily for early stages of diabetic retinopathy. One patient, not listed in this series because of imcomplete postoperative information, suffered secondary retinal detachment following her second session of light coagulation. A scleral buckling procedure was necessary to reattach the retina.

Our statistics suggest better results when photocoagulation is performed in an earlier stage of the disease. As visual acuity drops below 20/60, it appears from this series that chances of slowing progression of the disease are reduced.

Although our visual retention index is reasonably good, we cannot compare these results with those of cryohypophysectomy patients, since their selection is not comparable.

Why pituitary surgery or photocoagulation impede the progress is uncertain. Speculation centers on growth hormone being involved when the pituitary gland is ablated. Photocoagulation, on the other hand, would logically appear to have a more direct effect on the bleeding of vessels. Both forms of therapy are aimed at decreasing the incidence of hemorrhage.

Although retention of macular vision is important in considering the treatment of any retinal disease, the presence of macular damage does not rule out consideration of light coagulation in an attempt to save some retinal function. Taking into account the catastrophic results if diabetic retinopathy is allowed to progress and the desire of the patients to retain any vision, one should give serious consideration to halting progression of vasoproliferation and bleeding.

When using light coagulation to treat retinopathy, recurrence of hemorrhage should be treated immediately if the hemorrhage is not extensive. Often the new source of bleeding occurs in a previously treated area or at the edge of a previous light coagulation burn.

A few new areas of vasoproliferation or new, small dark hemorrhages following light coagulation can be observed rather than be considered for immediate additional treatment.

The best candidate for photocoagulation is the one who fulfills the criteria we now use for cryohypophysectomy insofar as systemic involvement and control of his disease. Photocoagulation appears to be most effective in treating discrete areas of retinal bleeding and new vessels. More than one session of photocoagulation may be necessary.

We recommend the use of photocoagulation when the stage of the disease is approximately the same in each eye. However, if the patient has lost useful vision in one eye, we tend to consider not more than one treatment session with photocoagulation in the better seeing eye. Should rebleeding occur, we then suggest pituitary surgery. If the patient does not meet the criteria for pituitary surgery, additional photocoagulation may be considered.

In the presence of a significant amount of vasoproliferation or fibroproliferation extending into the vitreous, we limit the amount of photocoagulation or offer cryohypophysectomy as our procedure of choice; photocoagulation may result in increased retinal traction and detachment.

Evaluation of the preoperative and postoperative findings by the O'Hare Classification [1] shows a higher incidence of the N_1 classification and a lower incidence of the N_2 classification in the postoperative patients. There appears to be no significant difference in the fibroproliferation classifications preoperatively and postoperatively. In the

[1] See O'Hare Classification, p. xxi.

postoperative patients there is an increased incidence of "no hemorrhage" as compared to this classification preoperatively. The hemorrhagic components are also decreased postoperatively.

CONCLUSIONS

We stress the importance of a team approach and of seeing patients early enough to consider suitable therapy. Photocoagulation for diabetic retinopathy in a series of 32 patients and 46 eyes appears effective in the earlier stages of the disease. As visual acuity drops below 20/60, chances for slowing progression of the disease decrease. Vasoproliferation and bleeding areas are treated by photocoagulation. If possible, treatment in the macular area should be avoided, but when most of the disease centers in these regions, photocoagulation should be considered. When the patient has useful vision in only one eye, we are reluctant to advise more than one session of light coagulation; if rebleeding occurs, we consider pituitary surgery. Photocoagulation and cryohypophysectomy should be thought of together in approaching the problem of diabetic retinopathy, not as if they were independent of each other.

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CHAPTER 44

Photocoagulation of Diabetic Retinopathy (A Rationale)[1]

HAROLD F. SPALTER, M.D.

In 1960 Meyer-Schwickerath (*1*) reported on the application of his newly introduced light coagulator to the destruction of the abnormal vessels which dominate the clinical picture of diabetic retinopathy. The few cases treated were very advanced, beyond the call of realistic hope, and therefore his initial results were poor. But the rationale of destruction of the abnormal retinal vascular patterns in diabetes remained attractive to a few clinical investigators in this country who had been recently trained in the use of the xenon arc photocoagulator.

Probing reports appeared in 1963 by Wetzig (*2*), followed by Thornfeldt (*3*) and Okun (*4*), and a new dimension was added to the therapy of diabetic retinopathy. It is to this mode of therapy that I should like to devote the remainder of this paper, for it is this approach to which we are now applying our energies at the Institute of Ophthalmology at Columbia.

In order to evaluate what to treat and the effects of treatment, a careful pictorial followup of the evolution of the disease in each individual is strongly recommended. Fundus photography and ideally fluorescein studies, when available, should be used to compile a visual history of the individual patient's disease. Fluorescein by virtue of its high-contrast capabilities may reveal more of the pertinent pathology than routine ophthalmoscopy or color photography. Higher power magnification of the photographs can be advantageous by allowing a more detailed study of the host of pathologic patterns which must be identified before they can be treated.

Once having graphed the pattern and progress of the disease we should then establish a rationale upon which to base the photocoagulation treatment. This is important, for without a blueprint for therapy, without guidelines to lead us through the maze of multiple manifestations of diabetic retinopathy, treatment would be hit or miss and not subject to future evaluation.

The principles we are currently following are summarized in table 1. One may note that the only positive statement in the list is the first,

[1] See Appendix M for raw data on individual patients.

From the Department of Ophthalmology, Columbia-Presbyterian Medical Center, College of Physicians and Surgeons, New York, N.Y. This work was supported by USPHS grant No. 07130.

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TABLE 1.—*Photocogulation of diabetic retinopathy*

Rationale:
(1) Improve metabolism.
(2) Prevent hemorrhage.
(3) Prevent retinitis proliferans.
(4) Limit and/or prevent retinal detachment.
(5) Resist vitreous contraction.

the highly speculative concept of improvement of metabolism. The remainder of the major principles of treatment are designed to thwart the already established or imminent problems such as hemorrhage, detachment, etc.

Hopefully, improvement of the retinal metabolism in the absence of a more definitive attack on the underlying systemic metabolic problem of diabetes mellitus may indeed prove to be the most promising of these several roads of treatment to follow. One aspect of this approach is to improve retinal circulation by photocoagulating the pockets of blood stasis, the microaneurysms, which in turn identify the shunt vessels. Many investigators believe that these vessels, by abnormally connecting arteriole to venule, deprive more peripheral areas of nutrition. It is suggested that this early interference with metabolism leads to the later stages of retinopathy manifested by neovascularization and hemorrhage. Flat preparations of the retina demonstrate that the capillary bed adjacent to shunt vessels is often not perfused thereby leading to anoxia with release of "vasoformative" factors and consequent retinopathy. Although high-speed fluorescein studies (*5*) have recently cast some doubt on this hypothesis, it still remains an attractive working concept.

Because of the possible metabolic deprivation of vital retina by these abnormal shunts some investigators have suggested the more radical approach of destroying the peripheral retinal arterial supply. This is hoped to maximize the circulation to the posterior pole thereby assuring the macula of adequate metabolism and preventing this vital retinal area from being bypassed. An alternative method reducing the retina's total metabolic needs is random photocoagulation of large areas of peripheral retina. Partial support for the validity of these concepts may be found in the evidence of minimal retinopathy (hypertensive, diabetic) on the side of a previously established carotid artery occlusion. In addition, recent observations of asymmetric diabetic retinopathy in patients with unilateral optic atrophy add credence to the concept of the beneficial influence of reduction of ocular blood flow on the retinal vascular manifestations of diabetes.

To continue on then in our analysis of the rationale of photocoagulation of diabetic retinopathy: preventing intraocular hemorrhage from any site would be advantageous; preventing proliferans in its earliest

manifestations in hopes of aborting the final phase of proliferans, retinal detachment, is essential; and finally to resist vitreous contraction (*6*) (when it is visibly manifest as local adhesions beginning to avulse or elevate the retinal vessels into the vitreous cavity) which may be most important in retarding the pathogenetic sequence of diabetic retinopathy.

If this summarizes the philosophy of photocoagulation therapy, what are the practical applications? What are the specific retinal lesions to be treated?

Destruction of random areas of peripheral retina by photocoagulation is accomplished quite easily if the media (lens, vitreous) are clear. However, the most peripheral portion of the retina is often not easily visualized with the currently available photocoagulation apparatus (xenon arc and laser). For these peripheral regions, retinal obliteration may be achieved more readily with transcleral cryopexy. With this modality noncontiguous treatments from ora serrata to equator can be performed without conjunctival incision.

Microaneurysms are easily destroyed. Neovascularization on the retinal surface is most amenable to coagulation as are the vessels which serve the areas of proliferans and are often the source of vitreous hemorrhage. The feeder vessels of proliferans, unfortunately, however, are often lost ophthalmoscopically as they reach into the glial thickenings within the vitreous. Fluorescein studies here serve a dual purpose, in some cases, of first identifying the feeder vessels. Secondly, pooling of the fluorescein through leakage from the abnormally permeable vessels may permit more effective absorption of the photocoagulation energy, even though the vessels are elevated from the underlying pigment epithelium.

Photocoagulation of intact retina surrounding localized areas of retinitis proliferans (fig. 1) may abort the development of retinal detachment due to the persistent vitreous traction. Several areas may be treated and low energy output by the photocoagulator is important to avoid unnecessary heating of the vitreous.

Photocoagulation may also play an important role to prevent extension of an already established retinal detachment. Such detachments often have no detectable retinal holes and surgical repair is contraindicated. One patient, recently treated, presented with a slowly extending detachment associated with retinitis proliferans in her only eye. No retinal tear was visible. Progressive field loss threatened the little, though useful, peripheral vision that remained. Photocoagulation at the borders of the detachment, a 360° barrier, has preserved the peripheral vision for almost a year and is still intact (fig. 2).

Finally, treatment of subhyaloid hemorrhages may hasten absorption of the hemorrhage. An ancillary benefit may be the destruction of the

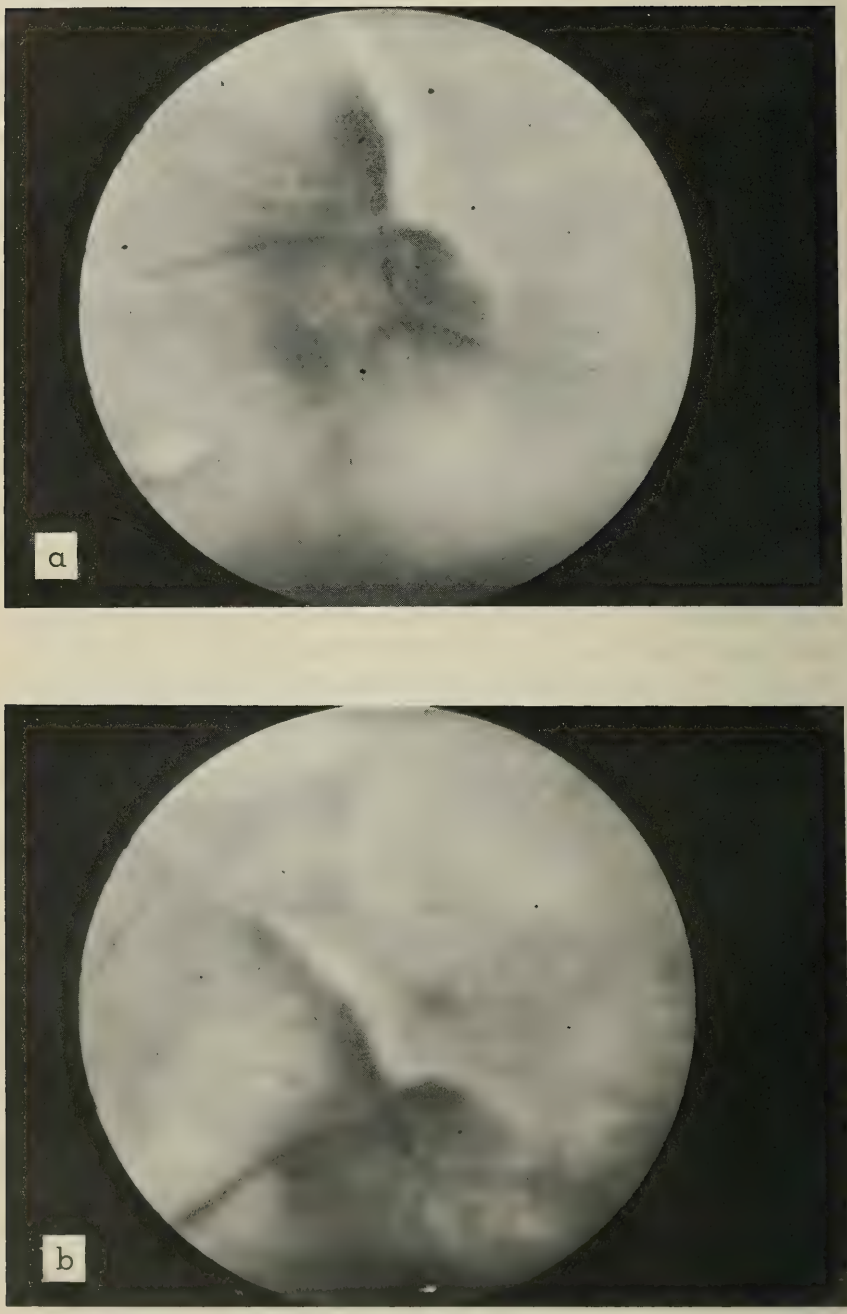


FIGURE 1.—*Photocoagulation of localized area of retinitis proliferans (reproduced from kodachrome).* a. *Prephotocoagulation.* b. *12 hours post-photocoagulation.* c. *4 months post-photocoagulation.*

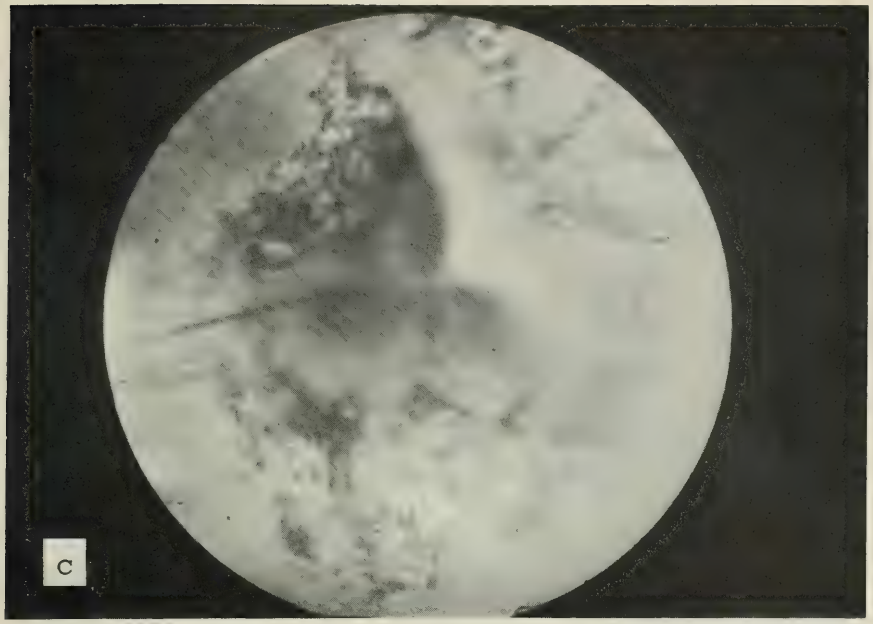


FIGURE 1c

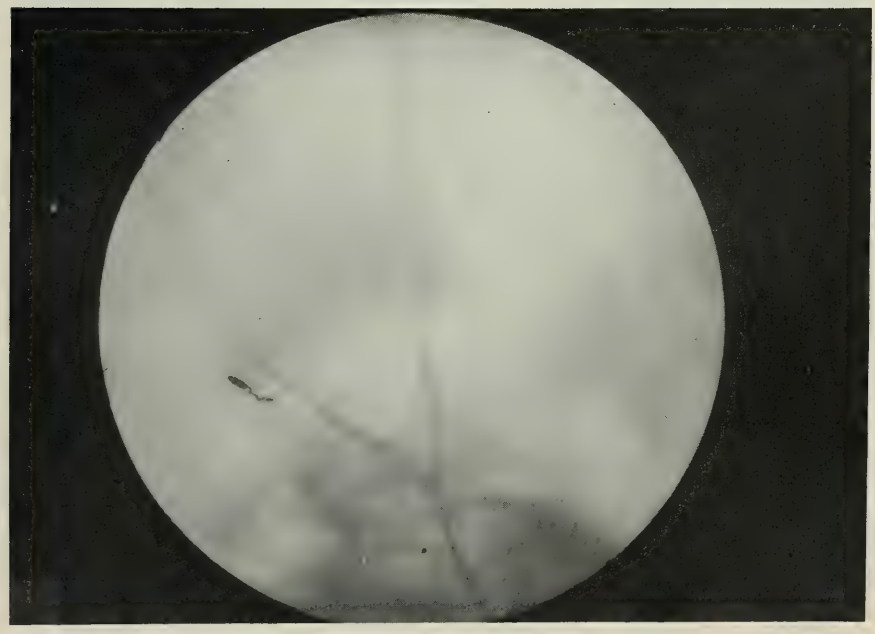


FIGURE 2.—*Delimiting barrier of photocoagulation in diabetic retinal detachment. (Reproduced from kodachrome). Note double row of xenon arc coagulations at border between detached retina below and intact retina above.*

underlying vessels which have produced this hemorrhage. These hemorrhages which threaten to penetrate into the vitreous with resultant prolonged visual loss respond remarkably well to low intensity photocoagulation. As shown in figure 3, coagulation is quite evident in the blood cell mass within a few minutes of treatment. Within 3 days denaturation of the red cell proteins has occurred, followed in 1 to 2 weeks by disappearance of the hemorrhage.

The treatable lesions cited in the preceding paragraph must be counterbalanced with the diabetic retinal pathology too often seen which is not amenable to photocoagulation therapy. These nontreatable lesions include neovascularization of the disc, total retinal detachment, diffuse vitreous hemorrhage, and neovascularization in the vitreous. We may be able to question whether the last group should remain in this list. As previously mentioned, judicious use of fluorescein permits sufficient pooling in some cases to allow sufficient coagulation energy to destroy these intravitreal vessels.

A separate manuscript would be necessary to give adequate consideration to the important subject of the potential hazards of photocoagulation. In very brief summary, one must cite the possibility of

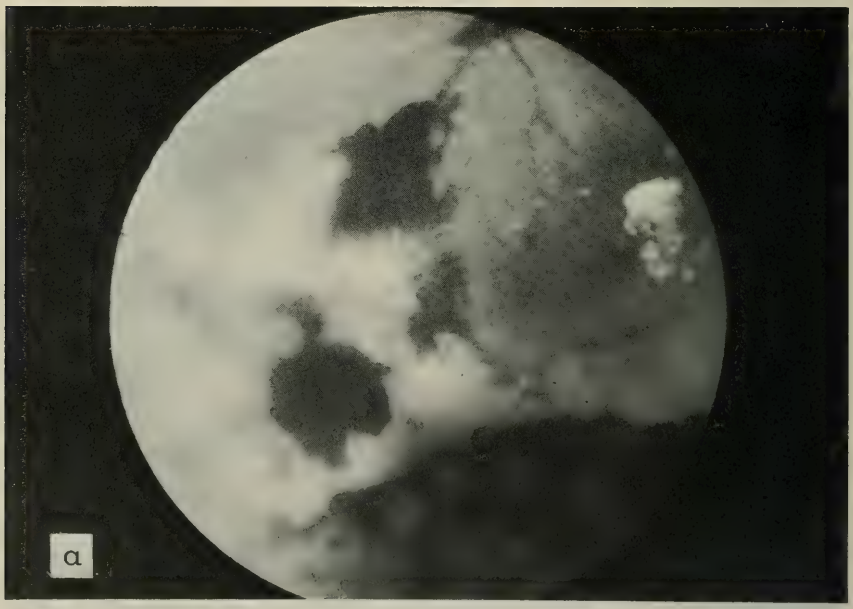
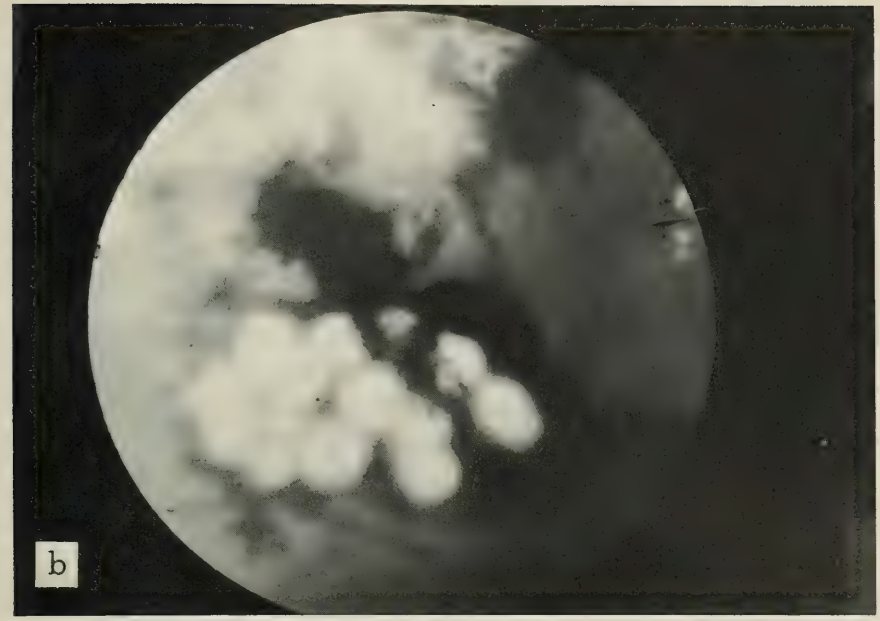


FIGURE 3.—*Photocoagulation of subhyaloid hemorrhage (reproduced from kodachrome). a. 5 minutes after xenon arc photocoagulation of red cell mass (in lower third of photograph). Note also exudates in macula as reference point. b. 1 day post-photocoagulation. c. 4 weeks post-photocoagulation. Note complete absence of hemorrhage with no evidence of coagulation scars in the underlying retina.*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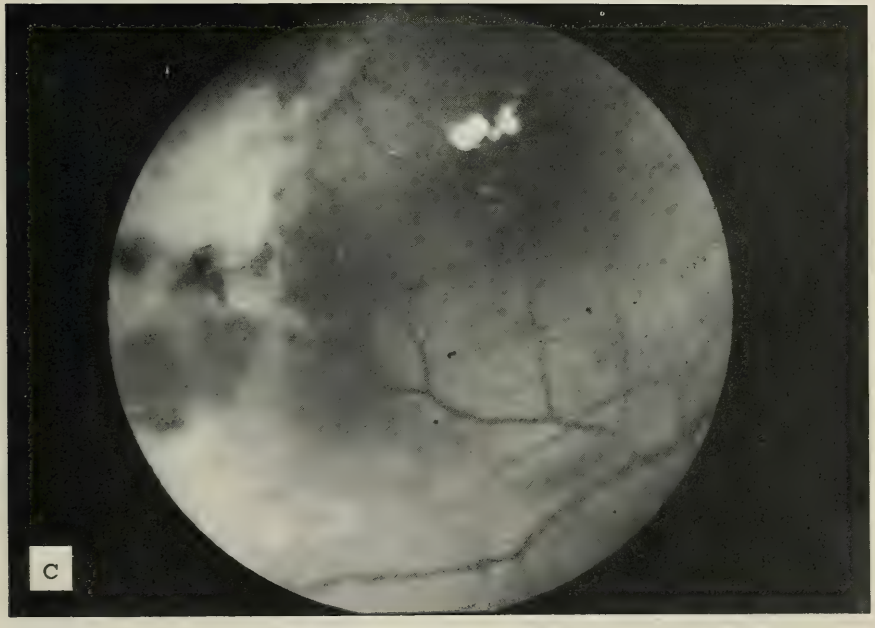
c

inadvertent coagulation of the macula, unexplained distortion of the macular architecture by photocoagulation at distant sites, excessive internal heating of the vitreous with formation of traction bands, production of retinal tears, and hemorrhages secondary to overtreatment are a few highlights of iatrogenic disease which must be constantly borne in mind. The experience of the ophthalmologist with the disease entity becomes critical and his familiarity with the use and abuse of the photocoagulation apparatus mandatory.

The currently used photocogulators for this work are the xenon arc Zeiss coagulator and the ruby laser photocoagulator. Because the red spectrum of the ruby passes freely through blood without significant absorption, this instrument is not effective in the destruction of abnormal vessels but is useful in treating intact retina. The clinical problem will dictate whether the xenon arc or laser coagulator is required. We have found that for the great bulk of our diabetic work the Zeiss xenon arc coagulator is the instrument of choice.

New instruments are being evaluated in a continuing attempt to improve our therapeutic armamentarium. Comberg's recently developed xenon arc photocoagulator (manufactured by Zeiss of Jena in East Germany) has an energy spectrum potentially greater than the standard Zeiss machine and a binocular viewing system which may improve visualization and focusing within the eye.

On the horizon but not yet available are argon lasers whose wavelength is specific for blood vessel destruction and thus may add another useful tool for the therapy of diabetic retinopathy. Finally, at Columbia, in addition to evaluating new xenon arc and laser coagulators, another form of energy, ultrasound, is being explored for its application in the ocular problems of diabetes. The use of ultrasound is now being refined to a high level of control so that its energy output may be used in therapy in addition to the more conventional diagnostic problems. By liquefying the vitreous of diabetics with ultrasound it is theoretically possible to abort the whole constellation of retinitis proliferans. Animal experiments have established the rate of absorption of radioactively tagged autologous blood in the vitreous (7). In rabbits whose vitreous was exposed to focused ultrasound prior to injection of blood, preliminary data reveal a 50-percent increase in the rate of blood absorption. Such data are exciting but the final hardware to test the theory in man may still be years away.

To conclude, it may be fairly stated that until diabetes is eliminated or until the vascular complications are better understood and dealt with at the molecular or biochemical level, we may have to rely on all the aforementioned rather gross mechanical means of destruction of abnormal tissue in the retina and vitreous. By photocoagulation at best

we are employing a stopgap measure; at worst, the test of time may tell us that our energies in this area have been wasted. But until the basic problems of diabetes are solved, it is our obligation to continue the attack on blinding retinopathy with whatever reasonable means are available.

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CHAPTER 45

Photocoagulation for Retinitis Proliferans

PAUL R. THORNFELDT, M.D.

It is with great pleasure that I share my experiences of 8 years of photocoagulation for diabetic retinopathy. It is also of personal satisfaction to find that there is a great deal of interest in photocoagulation, for only recently has this modality of therapy become generally recognized for its value in the care of patients with proliferative retinopathy.

The series of cases presented in this paper presents other facets which should be taken into serious consideration before photocoagulation is chosen as the treatment of choice.

The economic difficulties of patients are often discussed very little, but this average age is usually the period of maximum responsibility: payments on house, car, color TV, and education of children. The length of time diabetic demonstrates again that proliferative retinopathy is really the retinopathy of the juvenile-onset diabetic. It is my feeling that the elderly patient who has diabetes of relatively short duration and subsequently develops neovascularization, probably develops this on the basis of retinal vein occlusion rather than true diabetic neovascularization.

Number of patients	292.0
Average age	48.3
Oldest patient	74.0
Youngest patient	19.0
Average length of time diabetic	24.7
Least years diabetic	3.0
Most years diabetic	44.0

The relationship of control to development of retinopathy is often questioned but control has been a definite factor in this series, and appears to be almost as much a factor as length of time of diabetes. A significant number of these patients are "brittle" diabetics and it has been difficult at best to understand why a patient who has always taken excellent care of his diabetes with the same philosophy of management suddenly went "sour," and despite all efforts by the patient and the diabetologist, ultimately expires. Certainly, at present our knowledge of diabetes is only fragmentary with much original thinking needed.

Attempts were made in this series to correlate retinopathy with nephropathy using various kidney function tests, but the only constant finding was that there was no hand-in-hand relation. One finding

of significance was that there was a definite diurnal variation in the renal threshold for glucose with the threshold being higher in the morning, which is of great importance in consideration of control. In general, it was found that the patients responded better to split doses of insulin, with the amounts being quite predictable for both males and females. The importance of adequate education of the patient was a most significant factor, with the most common mistake being in the manner in which the patient injected insulin. Criteria for good control are almost as hard to establish as a simple classification for retinopathy. No attempt was made to classify the patients in this series by the O'Hare Classification (page xxi).

The technique of photocoagulation is well established and this series were all done by the author with local anesthesia being used routinely. All forms of retinopathy were coagulated with a multitude of complications. In general, iritis of varying extent was quite common, along with keratitis, vitreous hemorrhages, retinal and vitreous traction, especially as higher intensities and more extensive disease were treated. Out of the nearly 300 patients, the most serious complication which has occurred to date is in a patient who developed an arterial occlusion on one side and a massive vitreous hemorrhage on the other side, with a minimal amount of coagulation.

At the present time, it is the author's opinion that photocoagulation should be confined to neovascularization flat on the retina, or in early band formation. Attempts at massive band formation generally have been quite unsuccessful and may have produced more harm than good. Coagulation of tufts extending forward into the vitreous from the disc have been spectacularly unsuccessful despite the use of fluorescein. The incidence of complications has been quite high in attempting to destroy lesions close to the macular area and it is the author's opinion that this should be done with great temerity. Unfortunately, lesions seem to be most common along the course of the superior temporal vein. Laser coagulation, using the ruby rod laser, was much less successful than the Zeiss coagulator and the laser has been abandoned.

The question as to how much should be coagulated is often difficult, but this has always been applied to proliferative disease. Attempting to destroy microaneurysms and retinal hemorrhages, or attempting to destroy all the lesions seen with fluorescein has not been done because the author considers this to be shooting sparrows with a cannon.

A review of the first 30 patients coagulated in 1961 and 1962 gives some interesting food for thought. Out of the 30 patients, 23 are now dead, which is a 76 percent mortality rate. One patient has disappeared, but out of the six survivors, only two are gainfully employed. Three

are completely blind, and interestingly enough, their diabetes is much easier to control than when they had sight.

The high incidence of emotional disturbance associated with the juvenile diabetics is a very well recognized fact and this has been a constant finding in this series. The emotional response of patients who have undergone repeated coagulations should be given serious consideration in deciding as to the importance of further coagulation.

In summary, photocoagulation has a very definite place in the treatment of retinitis proliferans, but also has its definite limitations. This appears to be a striking situation in which an expert can treat a patient with a lesion of unknown cause, in a disease of unknown etiology, by a procedure whose mechanism of action is also unknown, all of which speaks well of the scientific approach to this problem. It is the author's opinion that both photocoagulation and pituitary ablative procedures should be recognized as palliative procedures.

CHAPTER 46

Vitreous Studies in Diabetic Retinopathy Treated With Photocoagulation[1]

W. A. J. VAN HEUVEN

The importance of the vitreous in the pathogenesis of visual loss from diabetic retinopathy is well known. (*1*, *2*). Therefore, it seems reasonable to study the vitreous pre- and postoperatively, with the best instruments available, in any evaluation of operative results. Only by doing vitreous studies together with retinal examination can we expect to find at what stage of the diabetic process we are performing our surgery and whether this surgical intervention truly changes the natural course of progressive loss of vision.

Examination of the vitreous today is best performed with the Haag-Streit model 900 slit lamp and the Goldmann three-mirror contact lenses. (*3*). The Haag-Streit slit lamp derives its versatililty from a rotating slit which can be oriented in any meridian and an illuminating column of variable inclination, so that all horizontal, oblique and vertical optical sections can be seen three dimensionally. The new Goldmann three-mirror contact lens gives a larger retinal and vitreous field of view than any other available contact or precorneal lens. Using these instruments, a vitreous classifications of slit lamp findings can be superimposed on the O'Hare Classification [2] of ophthalmoscopic findings.

The patients under discussion fall into the O'Hare H_0 or H_1 groups. H_2, by definition, precludes vitreous as well as retinal examination. H_1 is a very broad group, including all patients with ophthalmoscopic evidence of blood in the vitreous. H_0 presumably includes only patients without vitreous blood. Thus, it is interesting to note that H_0 becomes smaller as our instruments for vitreous examination become more refined. Many eyes with no ophthalmoscopic evidence of blood in the vitreous indeed show red blood cells with the slit lamp and contact lens. This finding suggests that the ophthalmoscope is not the best instrument available for making a meaningful interpretation of the amount of blood present in the vitreous cavity.

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[1] The eyes discussed in this paper are the same as those presented by McMeel and Van Heuven in "Photocoagulation as a Treatment of Diabetic Retinopathy" (ch. 40).

[2] See O'Hare Classification, p. xxi.

From the Retina Service of the Massachusetts Eye & Ear Infirmary. This work was supported by the U.S. Public Health Center grant No. NB–05691 from the National Institute of Neurological Diseases and Blindness, National Institutes of Health, U.S. Public Health Service.

We, therefore, graded the amount of vitreous blood on the basis of slit lamp findings from none to 4+ as follows: trace equals few enough RBCs to count; 1+ equals too many RBCs to count but vitreous not filled with RBCs; 2+ equals thousands of RBCs diffusely dispersed; 3+ equals RBCs obscuring vitreous detail; 4+ equals dense blood clot obscuring the retina (table I). We then correlated this with the course of the retinopathy after photocoagulation. The postoperative course was considered static if the retinopathy remained the same. Progression meant an increase in the retinopathy with or without visual change. Thus, some patients who experienced no change or even an improvement in visual acuity after photocoagulation were classified as having progressed if their retinopathy appeared worse.

Table II shows the results of photocoagulation. Of 33 eyes with 0–1+ blood in the vitreous, 64 percent remained static after photocoagulation while 46 percent of 48 eyes with 2+–3+ blood in the vitreous remained static. The difference in the two percentages is not statistically significant.[1]

Another method of vitreous classification, concerned with the presence or absence of vitreoretinal adhesion or traction, is more important (tables III and IV). Eyes in group I showed no vitreous detachment; eyes in group II showed partial vitreous detachment with vitreoretinal adhension in areas of retinopathy; and eyes in group III have total vitreous detachment. Eyes in groups I and III combined showed no marked vitreoretinal traction and comprised 38 eyes, whereas 53 eyes in group II showed traction. Of 78 eyes with a

TABLE I.—*Classification of vitreous blood as seen with slit lamp and contact lens*

None	No RBC's seen.
Trace	Few enough RBC's to count.
1+	Too many RBC's to count but not diffusely dispursed.
2+	Thousands of RBC's diffusely dispersed.
3+	RBC's obscuring vitreous detail but retina can still be classified.
4+	Dense blood clot obscuring retinal detail (same as O'Hare H_2).

TABLE II.—*Status 6 months after photocoagulation*

Vitreous blood	Static	Percent	Progressive	Percent	Total	Percent
0 to 1+ RBC	21	64	12	36	33	100
2+ to 3+ RBC	22	46	26	54	48	100

NOTE.—4+ RBC not photocoagulated.

[1] Determined by a Chi Square test at 0.05 level of significance (4).

TABLE III.—*Vitreous classification as seen with slit lamp and contact lens.*

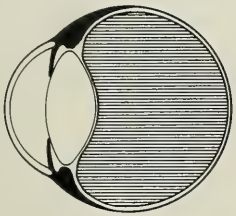
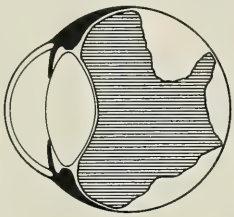
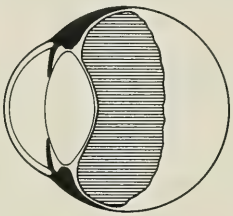
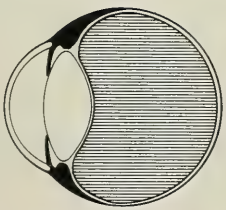
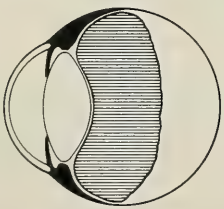
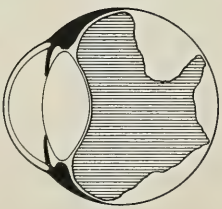
GROUP I	GROUP II	GROUP III
NO VITREOUS DETACHMENT *VITREOUS GEL FILLS VITREOUS CAVITY.*	PARTIAL VITREOUS DETACHMENT *VITREOUS REMAINS ATTACHED TO AREAS OF RETINOPATHY.*	TOTAL VITREOUS DETACHMENT *NO VITREOUS GEL ATTACHMENT TO AREAS OF RETINOPATHY.*
		

TABLE IV.—*Vitreous Classification as seen with slit lamp and contact lens.*

NO TRACTION		TRACTION
GROUP I	GROUP III	GROUP II
		

followup of greater than 6 months (table V), 70 percent of those without vitreoretinal traction did not deteriorate after photocoagulation, while only 36 percent of those with traction remained static after treatment. This difference is statistically highly significant.[1]

Thus, vitreoretinal adhesion was a useful factor in determining prognosis of diabetic retinopathy after photocoagulation. It could

[1] Determined by a Chi Square test at 0.05 level of significance (4).

TABLE V.—*Status 6 months after photocoagulation*

Vitreous	Static	Percent	Progressive	Percent	Total	Percent
Traction (II)	17	36	30	64	47	100
No traction (I and III)	22	70	9	30	31	100
Total	39		39		78	100

not be ascertained whether or not heat created in the vitreous by photocoagulation was enough to shrink the vitreous and thus increase traction on the retina. Certainly even the smallest amount of blood in the media requiring settings above green I on the Zeiss photocoagulator would increase heat absorption by the vitreous. This may have caused the vitreous shrinkage and secondary retinal detachment which one of our patients developed 8 weeks after photocoagulation. She had 2^+ cells in the vitreous and required a setting of green II with a field of 4.5° on the photocoagulator for adequate retinal burns. Other patients showing vitreoretinal adhesions before treatment may also have been influenced adversely by photocoagulation.

To summarize, this study emphasizes that vitreoretinal adhesions are ominous prognostic signs for patients whose diabetic retinopathy is to be treated with photocoagulation. These adhesions can often be missed by ophthalmoscopy alone. Vitreous study of all diabetics with slit lamp and contact lens is therefore necessary pre- and postoperatively to evaluate fully this mode of therapy.

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CHAPTER 47

The Treatment of Diabetic Retinopathy

ROBERT B. WELCH, M.D.

Today, we are faced with a disease which not only causes great morbidity and mortality among our population but often blinds them along the way. While we are controlling the metabolic deficiencies of diabetes, what can we do to help the ocular problem of diabetic retinopathy? What are our choices? Simply stated, they are: (1) Medical management and do nothing; (2) hormonal suppression (hypophysectomy); or (3) photocoagulation. Each of these disciplines has its proponents and its merits.

There is evidence that careful control may delay the onset and lessen the severity of diabetic retinopathy (*1–4*), and others have shown that diet low in animal fat may bring about reabsorption of lipid in the retina (*5*). Still others (*6*, *7*) have studied the natural course of the disease and have shown that approximately 50 percent of patients with proliferative retinopathy maintain good vision after 5 years (*8*, *9*, *10*). We, of course, are primarily concerned with the 50 percent who go blind (table I).

The proponents of hormonal suppression (*11*) have shown that hypophysectomy gives some benefit in approximately 60 percent of the cases over a 5-year period. But, the long term mortality rate, the problem of replacement therapy, as well as psychological problems should be considered (table II).

Photocoagulation has been used since Meyer-Schwickerath developed the light coagulator (*12*, *13*). Various reports (*14*, *15*, *16*) show

TABLE I.—*Medical management and do nothing*

A. Careful control may delay onset and lessen severity (*1, 2, 3, 4*).
B. Diet—low animal fat and corn oil (*5*).
C. Natural history of the disease.
   1. Thirty-nine eyes with early proliferative disease followed a benign course for 2 years (*6*).
   2. A 5-year study of nonproliferative retinopathy demonstrated that:
      Initial vision good (20/20 to 20/60) : 14.5 percent blind; 34.0 percent impaired vision; 51.5 percent good vision (*7*).
      Initial vision poor (20/80 to 20/200) : 50 percent blind.
   3. A study of proliferative retinopathy stated that 50 percent became blind OU within 5 years (*8*).
   4. In a study of 351 patients with proliferative disease followed 1 year or more, 47 percent had good vision initially. Of these 47 percent, 50 percent retained good vision after 5 years. Ten percent of the original group of 351 had a spontaneous arrest of proliferative changes (*9*).
   5. In proliferative retinopathy with loss of vision in one eye, a majority lost useful vision in the fellow within 1 year. Thirty-four percent maintained useful vision in the fellow eye 6 months to 12 years (*10*).

TABLE II.—*Hormonal suppression (based on Poulsen)*

A. Methods.
   1. Extirpative hypophysectomy.
   2. Stalk section.
   3. Radiation—implants.
   4. Radiation—transcutaneous.
   5. Thermal procedures.
   6. Adrenalectomy.

B. Stalk section data.
   Results in 110 patients followed 1 to 7 years (*11*) : 17 percent dead; 61 percent arrested; 41 percent regression; 8 percent failure. Of the group followed 5 to 7 years postoperatively (16 patients), 50 percent are dead.

C. Symposium. Influence of hypophysectomy and adrenalectomy on diabetic retinopathy. Diabetes. 11; 461–494. November–December, 1962. Eleven reports describing 134 cases.
   Hypophysectomy (103) : immediate surgical mortality, 11 percent. Stalk section (20) : long term mortality, 18 percent. Yttrium-90 (11) : some benefit, 63 percent.

vision stabilized in from 50 to 80 percent over periods ranging from 21 months to 7 years (table III).

At the Wilmer Institute and the Johns Hopkins Hospital the problem of diabetic retinopathy has taken two courses; pituitary surgery and photocoagulation. Pituitary procedures were begun in 1956. In the early group of patients (1956–64) there were no specific criteria for admission to the procedure. Thus, there was a heterogenous group of patients, some a poor risk, and others with advanced disease. Several surgeons were involved and various techniques were employed (table IV). As a result of studies on this group of patients, procedures other than total hypophysectomy were judged less reliable. Therefore, a new series was begun in 1964, under rigidly controlled criteria. A team of physicians was organized which included an internist, a neurosurgeon, and an ophthalmologist.[1] Several other ophthalmologists participated in the program as the series developed.[2] The basic criteria for the selection of patients were: (1) Useful vision in one

TABLE III.—*Photocoagulation*

A. Of 15 treated eyes: 3 improved, 10 unchanged, 2 worse (*12*).
   Of 11 untreated (fellow) eyes: 1 improved (2 year followup), 3 unchanged, 7 worse (*12*).

B. Of 111 patients with surface neovascularization and some intravitreal fibrovascular proliferation, 30 percent progressed (1 month to 5 years) and 70 percent remained stable (*15*).
   In a controlled study of 50 patients with symmetrical disease, 80 percent of the treated eyes remained stable whereas only 58 percent of the untreated fellow eyes remained stable during a followup period of 21 months (*16*).

C. Of 83 patients, 54 percent had stable vision, 24 percent had slow progression, and 22 percent had no benefit during a followup period of 1 to 7 years (*14*).

D. In one study, 90 percent of microaneurysms and 22 percent of flat neovascularization was obliterated with laser coagulation (*13*).

[1] Thaddeus E. Prout, Assoc. Prof. Med., JHH., George B. Udvarhelyi, Assoc. Prof. Neur. Surg., JHH. David L. Knox, Assoc. Prof. Ophthal., JHH.

[2] Robert B. Welch, Assist. Prof. Ophthal., JHH., David Paton, Assoc. Prof. Ophthal., JHH. Stewart M. Wolff, Assist. Prof. Ophthal., JHH.

TABLE IV.—*Pituitary procedures, 1956–64, Johns Hopkins Hospital*

Procedure	Number patients with primary procedure	Number patients with secondary procedure
Implantation (Gold)	9	2
Surgical hyphophysectomy	6	4
Stalk section	1	
Other implantation	2	
Total patients	18	

NOTE.—Results: 9, vision improved or no deterioration, 50 percent; 6, vision worse; 3, poor followup. Of patients improved, 8/9 had surgery either as primary or secondary procedure; 1/9 had implantation alone. No operative mortality.

eye, 20/70 or better, without severe proliferans, detachment, or glaucoma (no worse than $N_1F_1H_1$ O'Hare Classification)[2]; (2) history of recent progression of visual impairment, usually with loss of vision in one eye as evidence of advance of disease; (3) absence of significant complications that are life threatening (cardiovascular, renal, etc.). (Age has become a limiting factor and patients over 45 years are accepted only if extremely good candidates); (4) psychologically sound patients, capable of following a medical regimen and able to understand the risks and problems; and (5) support and cooperation of local medical authority. It is unwise to do the procedure and have the patient followed by a local physician fearful of the problem of management or hostile to the situation. Under these criteria, 15 patients were operated between 1964 and 1968. The results are tabulated in table V.

Photocoagulation was begun in 1962. The criteria for treatment were, in large part, based upon my previous experience with the use of diathermy in an attempt to wall off diabetic detachments or treat proliferative retinopathy and my observations of a number of cases of advanced retinopathy treated by photocoagulation. Since these efforts were uniformly unsuccessful, it was decided to treat only cases with very early neovascularization and without proliferation into the vitreous unless they were isolated, small and away from the macula. Cases with proliferation off the disc, tented up retinas, or fibrous proliferation into the vitreous of any extent were excluded. To date, 15 cases fulfilling these criteria have been treated. They have uniformly done well. On the other hand, nine advanced cases treated at the Institute by other investigators have uniformly done poorly (table VI). Based on these poor results of advanced cases as well as cases seen at the Retina Clinic, I have attempted to find early cases for treatment. Unfortunately, the majority of cases sent to me for consultation are turned down because, in my opinion, the retinopathy is too advanced.

[1] O'Hare Classification, p. xxi.

TABLE V.—*Hypophysectomy series, 1964–68, Johns Hopkins Hospital*

PROCEDURE: TOTAL SURGICAL HYPOPHYSECTOMY	
Results:	
Dead (13 percent)	2
Postop. coronary and perforated (stress) ulcer in recovery period	1
Resistant bacterial infection, 5 months	1
Lost to followup	1
Reviewed at 12- to 18-month intervals	12
Total patients	15
Vision improved or no deterioration (percent)	83
Followup:	*Dead*
1 year—12/12	0
2 year—8/10	0
3 year—6/8	0
Medical problems (renal)	2
Psychological pattern (poor social responsiveness)	2

All cases treated received photocoagulation with the Zeiss coagulator. The settings used were Iris diaphragm 1–4, image field diaphragm 3° or 4.5°, and regular load No. 1. No more than 180° of the retina has been treated at one sitting and multiple procedures have been planned to prevent overtreatment at any one period. Retrobulbar anesthesia has usually been given to insure immobility of the globe and to prevent discomfort, since many treatments are in the posterior pole.

The other type of case I have been interested in treating is the circinate lipid-aneurysm complex. These cases lose vision because of lipid deposition and/or retinal edema in the macula. The macula is usually on the circumference of the circinate lipid. In the center of the lipid ring one finds aneurysms and neovascular areas. Photocoagulation of these cases will cause reabsorption of lipid and disappearance of

TABLE VI.—*Photocoagulation, 1962–68, Wilmer Institute*

Classification	Number of cases	Followup, 6 months to 5 years
PERSONAL SERIES—ROBERT B. WELCH		
N_1 F_0 H_0	10	Status quo.
N_1 F_1 H_0	2	1 status quo; 1 lost to followup.
N_2 F_0 H_1	3	2 status quo (1 postop. bleed); 1 lost to followup.
Circinate lipid-aneurysm complex	8	6 improvement of vision.
OTHER INVESTIGATORS—WILMER INSTITUTE		
N_2 F_1 H_0	4	4 worse.
N_2 F_2 H_1	3	3 worse.
N_1 F_1 H_1	2	1 better, 1 worse.

edema. In some cases vision may be dramatically improved. To date, I have photocoagulated eight such cases with improvement of vision in six cases. The most profound change was one case which came from 20/400 to 20/40. One case improved to 20/70+. The others have improved to 20/200+. Two cases have not improved their vision in spite of reabsorption of lipid.

SUMMARY

Faced with the problem of diabetic retinopathy, we are presented with three possible courses of action: (1) medical management; (2) hypophysectomy; and (3) photocoagulation. It has been my approach to treat the disease early with photocoagulation when only surface neovascularization is evident (N_1 F_0 H_0). It is difficult to obtain ideal cases as most are referred after the patient gets into trouble and the retinopathy is usually more advanced. I have also treated a number of cases with the circinate lipid-aneurysm complex, photocoagulating the vascular abnormality and noting reabsorption of lipid. When this occurs in the macula, vision may improve after treatment. Finally, a study is continuing at Johns Hopkins on hypophysectomy. The study is small because of rigid criteria.

The final solution to the problem of diabetic retinopathy remains to be answered in the future. In the interim, we must strive to save vision with a regimen of treatment that creates the least amount of danger to the patient and the eye with the best hope for retention of sight.

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CHAPTER 48

Results of Photocoagulation in Diabetic Retinopathy

ACHIM K. WESSING, M.D.
GERD MEYER-SCHWICKERATH, M.D.

INTRODUCTION

The first cases of diabetic retinopathy were treated with photocoagulation in the years 1955–59. In his monograph in 1959 Myer-Schwickerath (*1*) described five treated cases. Four of them, which were in the proliferative stage, showed no improvement; one case, however, with microaneurysms and yellowish exudates showed a considerable improvement.

During the following years this treatment was continued with great reserve. The original aim was to prevent recurrent hemorrhages from microaneurysms and new-formed vessels. Another idea was to prevent retinal detachment by multiple coagulations. In spite of some very impressive results we remained skeptical for a long time. We know how difficult it is to judge the therapeutical effect of photocoagulation in a disease which is so different from one case to another and which might undergo a spontaneous regression.

At the same time other authors also recommended photocoagulation treatment of diabetic retinopathy (*2–11*).

In 1963–64 our coworker K. Schott (*12*) collected the whole material of the Essen eye clinic for the first time and reported the results at the German Ophthalmological Society in Heidelberg. At this time it was already obvious that the best results were achieved when photocoagulation was performed in early stages without proliferation into the vitreous. In the following years we directed our interests more and more to the treatment of early cases. This was recently reported by Meyer-Schwickerath in the Klinische Monatsblätter and in the American Journal of Ophthalmology (*13*).

METHOD OF TREATMENT

Most of our photocoagulations were performed with the Zeiss xenon coagulator. We usually coagulate microaneurysms and new-formed vessels in the level of the retina and, if present, small beginning

proliferations into the vitreous. The diameter of the coagulation is between 1.5° and 3°. The intensity of the coagulation is chosen in such a way that a slight whitish discoloration of the retina becomes visible. We usually keep away from the macular area approximately two DD. We try to avoid the papillomacular bundle but small coagulations in this area do not necessarily damage the central vision. If the coagulation is performed with a small field and low intensity the nerve fibers are not damaged.

If the diabetic changes are not too extensive the whole fundus is coagulated in one session. Two hundred to 300 coagulations may be performed. If the changes are rather advanced and extensive we prefer to perform the coagulation in two or three sessions. Most of the treatments can be performed as outpatient procedures. Only very advanced cases are treated as inpatients.

If the treatment is performed in the early stage, complications are extremely rare. If hemorrhages occur, they are very small. In those cases however, where proliferations in the vitreous are present, the danger of postcoagulative hemorrhages is increasing. A further complication is the occurrence of an exudative retinal detachment in those cases in which many coagulations are performed. This exudative detachment however usually disappears in a few days.

RESULTS OF TREATMENT

Through the end of 1967 we have treated 127 cases of diabetic retinopathy. Forty-four of them were male and 83 were female patients. Twenty-four were younger and 103 older than 40 years. Altogether 189 eyes were treated. These eyes are classified according to the O'Hare Classification.[1] We have put together the proliferative cases into the group N/F of this classification. The observation time lies in between 9 months and 7 years. The average observation time is 2.6 years.

Figure 1a shows the results of the treatment recorded according to the ophthalmoscopical finding. It is evident that the results in the groups B and BH_1 (those cases with a pure background retinopathy and little blurring by hemorrhage) are very favorable. Out of 49 eyes in group B, 19 showed complete regression of diabetic changes: disappearance of microaneurysms and yellowish exudates as well as retinal edema. In 25 eyes we found a certain amount of remaining diabetic changes (some microaneurysms and exudates). These changes

[1] See O'Hare Classification, p. xxi.

classification at last examination	classification prior to therapy: B	BH$_1$	N/F
O	19	19	4
B	25	43	7
BH$_1$	5	14	1
N/F	–	2	34
H$_2$/ø	–	2	14

FIGURE 1a

classification at last examination	classification prior to therapy: B	BH$_1$	N/F
O	9	1	1
B	4	15	–
BH$_1$	3	5	–
N/F	–	–	7
H$_2$/ø	–	1	2

FIGURE 1b

FIGURES 1a–1b.—*Results of photocoagulation in diabetic retinopathy.*
(a) *Duration of followup between 9 months and 7 years.*
(b) *Duration of followup more than 3 years:*
O =*no diabetic lesions.*
B =*background retinopathy without hemorrhages.*
BH$_1$ =*background retinopathy with small hemorrhages.*
N/F =*retinopathy with neovascularization and fibrous proliferation.*
H$_2$ =*massive hemorrhage.*

however are obviously less than at the beginning. In five cases only we found an increase in diabetic changes and the occurrence of new hemorrhages. Very similar are the results in group BH_1. Out of 80 eyes 19 became completely free of diabetic symptoms. Forty-three showed some remaining changes, but no more hemorrhages. Fourteen further cases remained unchanged, and altogether four eyes presented a deterioration.

In the group of the proliferative retinopathy N/F the results are quite different. The final results are much less favorable. Only 12 out of 60 eyes showed a doubtless improvement. In 34 eyes the tendency to proliferation remained unchanged, and 14 eyes became blind.

If we analyze only those cases with an observation time of 3 years or more (fig. 1b) we can see that the discrepancy between the results of treatment in the pure background cases and the proliferative cases is getting more and more evident.

The same is shown by analyzing the visual acuity in the nonproliferative and the proliferative cases. In the cases of group B (figs. 2a, 2b, 3a, and 3b) the visual acuity overall remains unchanged before and after treatment. Some single cases with loss of visual acuity are compensated by others with marked improvement of visual acuity. In contrast to this we find in the group N/F (figs. 4a and 4b) a marked trend to impairment of visual acuity.

In quite a number of cases the final result is practical or complete blindness. This tendency holds true for the diabetic retinopathy of young patients as well as for the old ones.

Complications are rare in the B group. They become more frequent however in the group N/F. In 129 cases of nonproliferating diabetic retinopathy there were only six cases with hemorrhage after photocoagulation. In the group N/F however 22 hemorrhages occurred in 60 treated cases; furthermore, four secondary glaucomas, three cases with exudative detachment and two cases with optical atrophy were seen.

It is remarkable that most of our patients did not realize the defects in the visual field which occur after photocoagulation. This is true even in those cases in which several hundred of coagulations have been performed. The recording of the visual field at the Goldmann perimeter showed in most cases a small and irregular restriction of the visual field (figs. 5a and 5b). Also in those cases in which a small and circumscribed coagulation had been performed close to the disc and the macula, large field defects do not occur.

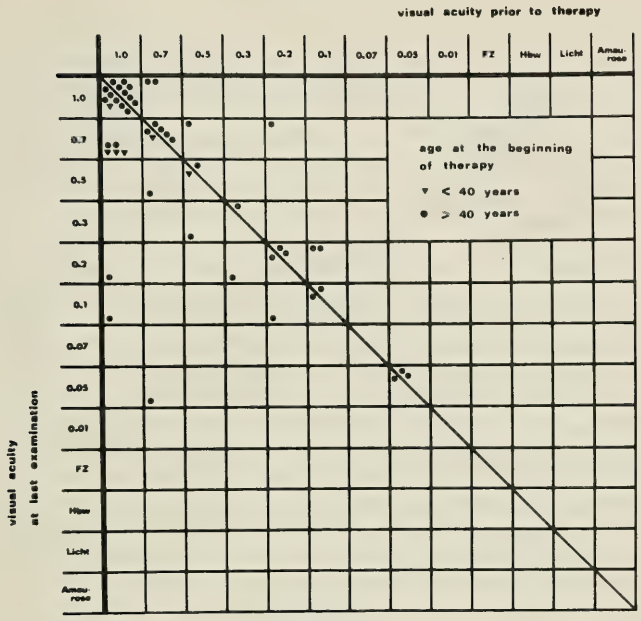

FIGURE 2a

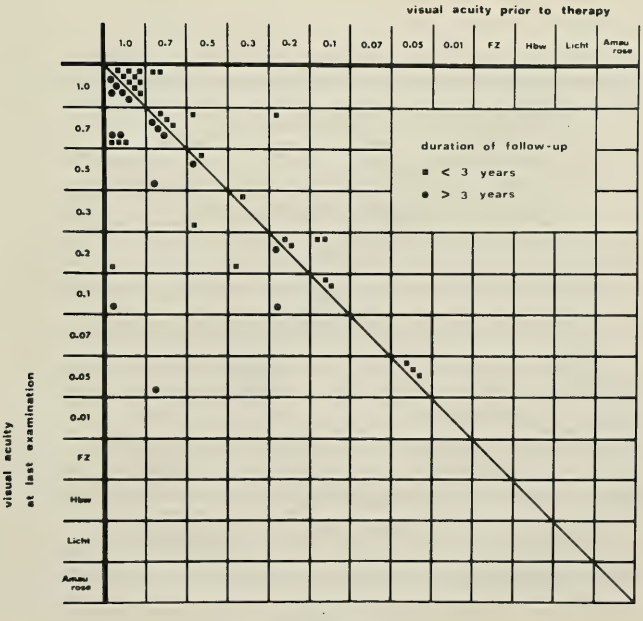

FIGURE 2b

FIGURE 2a–2b.—*Group B, visual acuity prior to coagulation and after coagulation. (a) Depending from the age of the patient. (b) According to the duration of followup.*

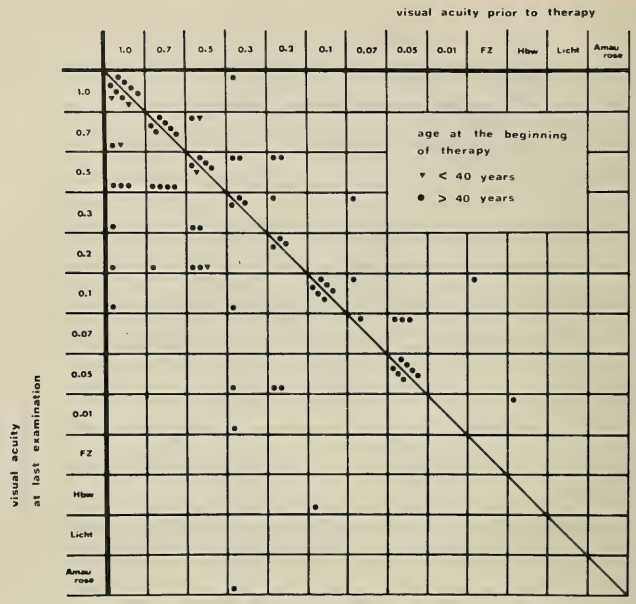

FIGURE 3a

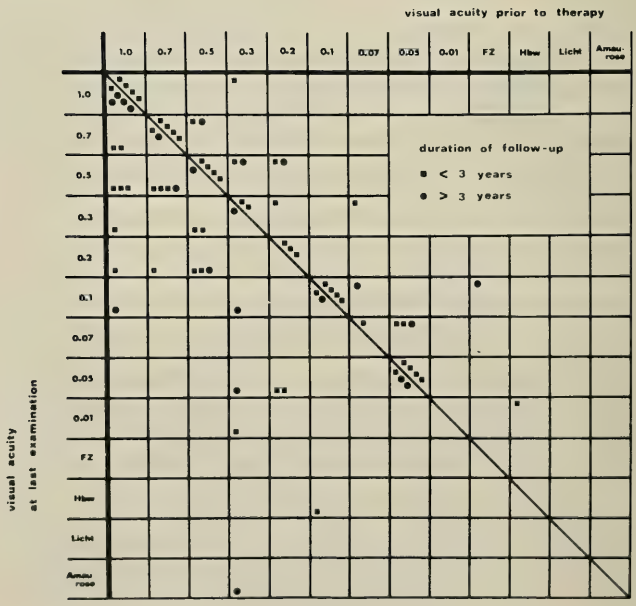

FIGURE 3b

FIGURES 3a-3b.—*Group BH_1, visual acuity prior to coagulation and after coagulation. (a) Depending from the age of the patient. (b) According to the duration of followup.*

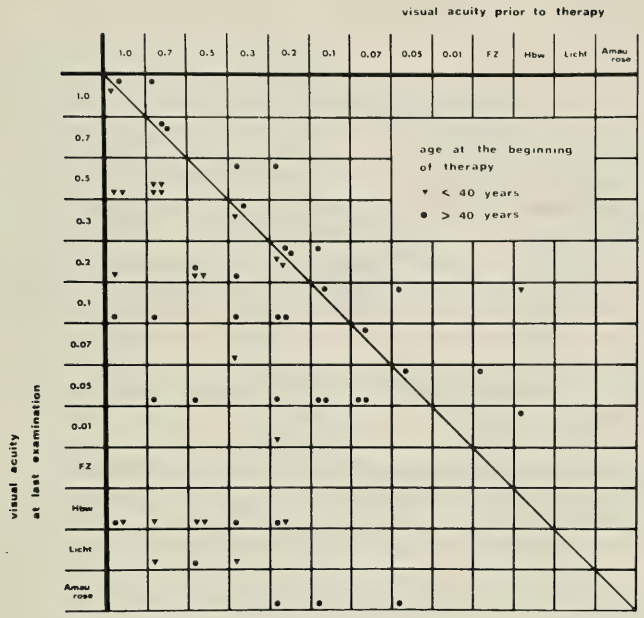

FIGURE 4a

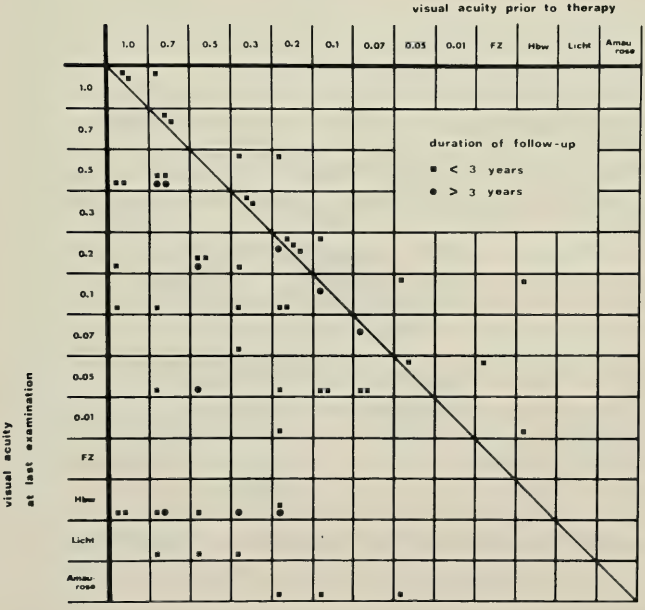

FIGURE 4b

FIGURES 4a–4b.—*Group N/F, visual acuity prior to coagulation and after coagulation. (a) Depending from the age of the patient. (b) According to the duration of followup.*

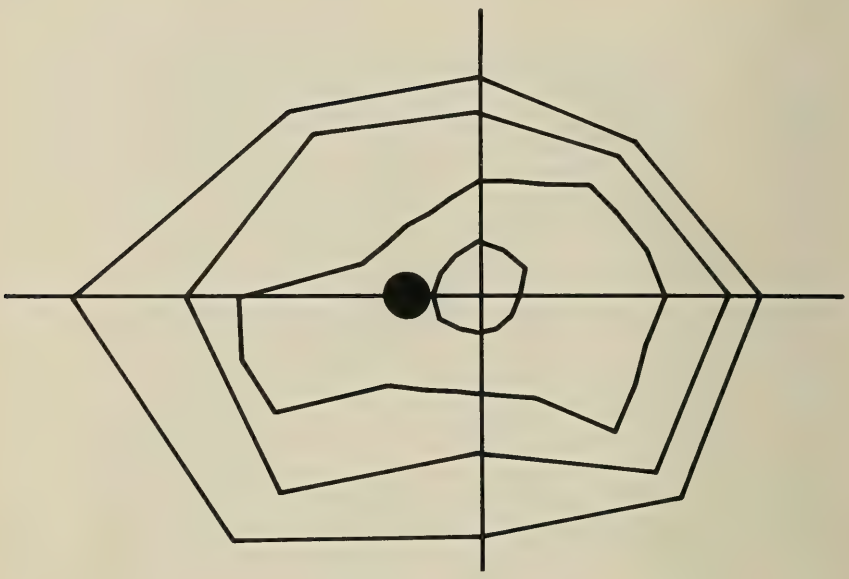

FIGURE 5a

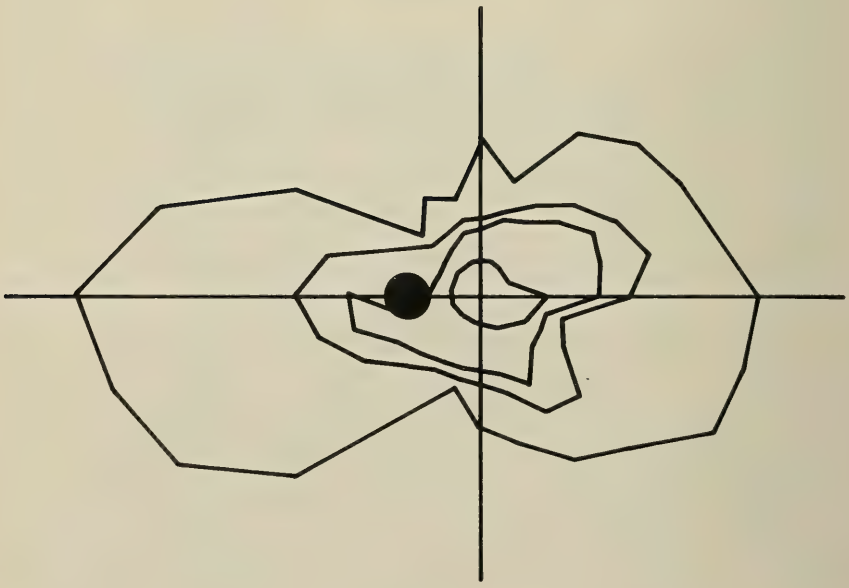

FIGURE 5b

FIGURES 5a–5b.—*Visual field (a) before (b) after coagulation.*

SUMMARY OF THE STATISTICAL ANALYSIS

The early symptons of diabetic retinopathy are reversible if photocoagulation is performed before a proliferation occurs. By treating early stages of the retinopathy the later proliferative stages with hemorrhages and retinal detachment can be prevented. If proliferative changes are already present at the time of treatment, the results of photocoagulation are less marked and more dangerous. In many cases photocoagulation comes too late and is not able to stop the progression of the disease.

LONGTIME FOLLOWUP BY PHOTOGRAPHY

It is very difficult to follow the changes in diabetic retinopathy over a long period of time by description of the fundi only. It is also difficult to classify the results only with central visual acuity, as we have mainly treated such cases which had quite a good visual acuity. To overcome this situation, fundus photography is of eminent importance. With the help of photography we can follow step by step even very small changes in progression or regression of diabetic retinopathy.

For this reason we had performed fundus photography in almost all cases in which it was possible, namely, in those cases in which there was no cataract and no severe hemorrhage of the vitreous. We went through our material over the last 12 years case by case projecting simultaneously the same areas of fundi one beside the other together with the report of diabetic control, performed photocoagulation, etc.

RESULTS

(1) Edema of the retina was present in most of our cases, even in those in which the visual acuity was still quite good. It can be seen in photographs that this edema hides, more or less, the pattern of the choroid. This retinal edema disapears slowly over months and years when sufficient photocoagulation has been performed.

(2) Microaneurysms and capillary dilatations in the level of the retina disappear when they have been coagulated.

(3) In the vicinity of coagulations, neovascularization disappears, even if not directly coagulated.

(4) With these changes the hard yellowish exudates disappear slowly, but continuosly.

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(5) The size, the engorgement, and the tortuosities of the veins decrease after treatment.

(6) The regression of all these changes occurs earlier in young people than in elderly patients over 50 years. Continuous improvement of all symptons can be observed even several years after treatment.

(7) After performance of photocoagulation it is extremely rare that proliferative retinopathy may develop.

The following case reports and fundus photographs should illustrate our observations (figs. 6–17) :

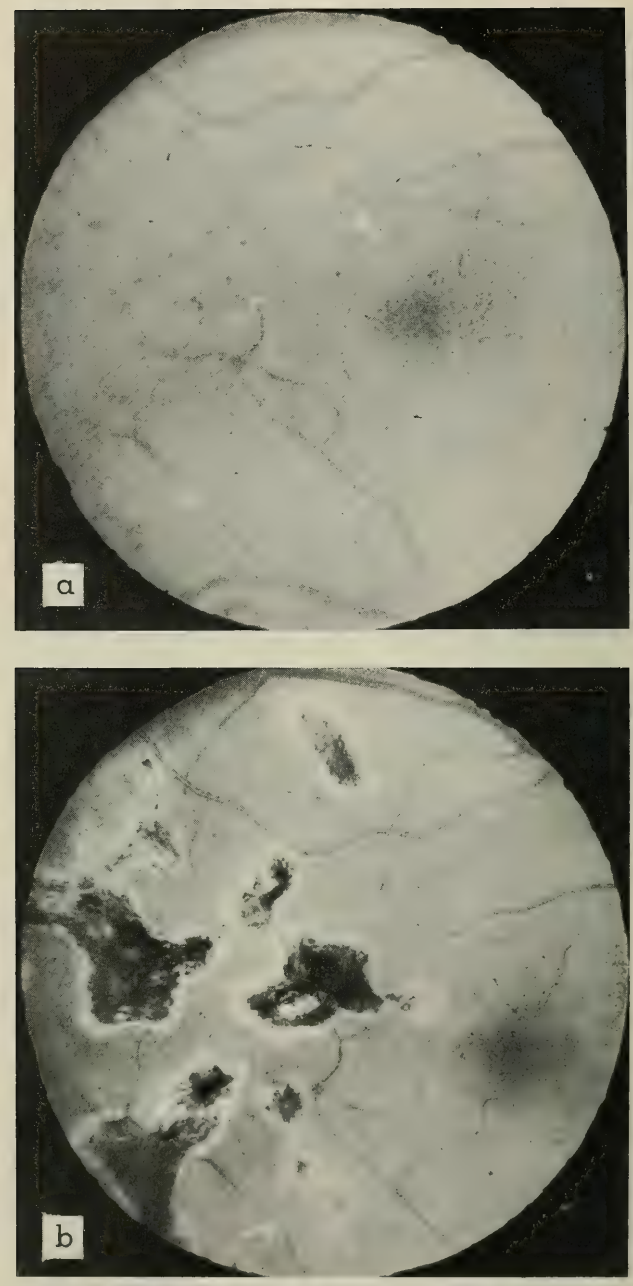
DISCUSSION AND CONCLUSION

We cannot explain how photocoagulation acts on diabetic retinopathy. It is doubtful whether the direct coagulation of microaneurysms and new-formed vessels is essential for the regression of the symptoms, as we have seen pathological vessels and microaneurysms disap-

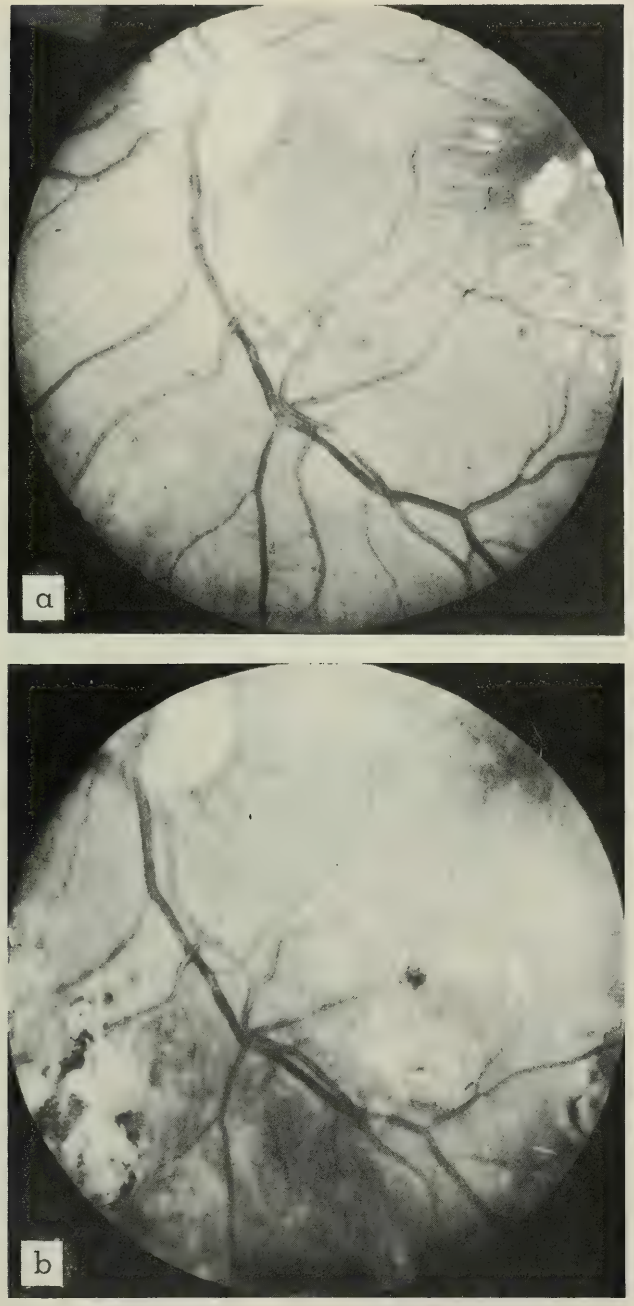
FIGURES 6a–c.—*Case 1: 33 year-old female patient with diabetes since 18 years, Figure 6a shows a mild diabetic retinopathy with exclusively background changes: Irregularities of the retinal surface, microaneurysms and small hemorrhages. Figure 6b shows the same eye 1 year later. Besides the coagulation scars one can see a decrease of the microaneurysms. Some yellowish deposits are still present. Figure 6c shows the same area 2 years later with further regression of all symptoms.*

b

c



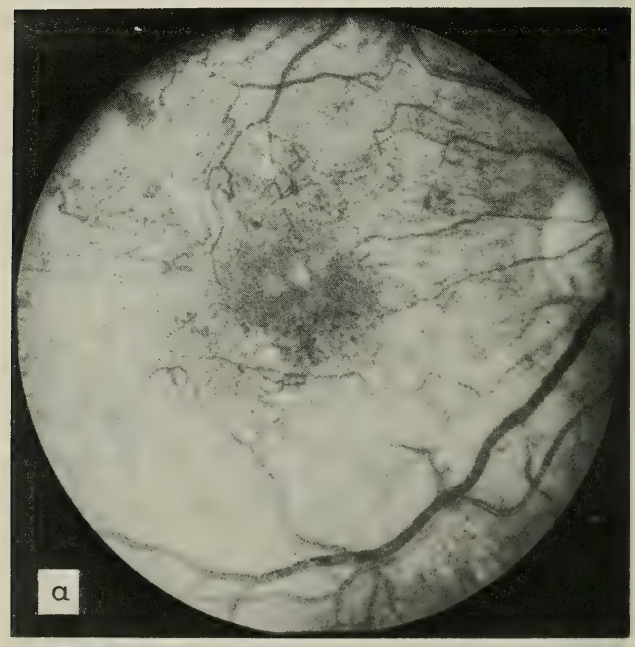
FIGURES 7a–b.—*Case 2: 40-year-old male patient with diabetes known since 5 years. Figure 7a, taken in 1964, shows the right eye before treatment with microaneurysms, yellowish exudates and retinal edema. In figure 7b one can see that all changes have nearly completely disappeared besides the dark pigmented coagulation scars.*



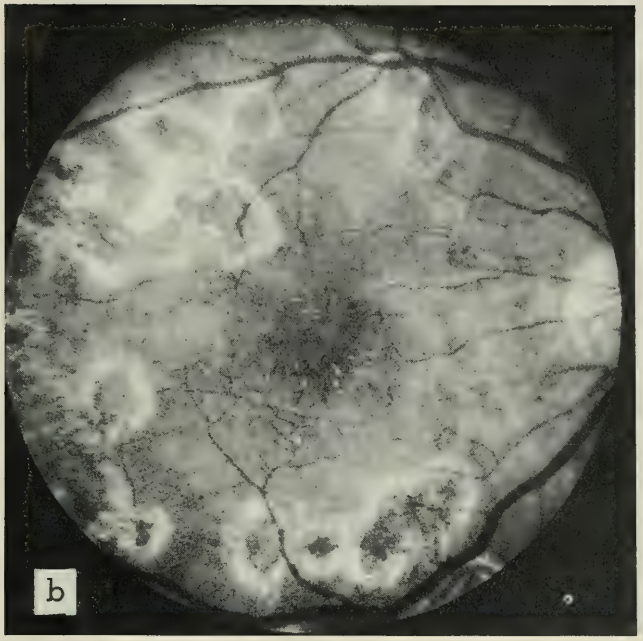
FIGURES 8a–b.—*Case 3: 27-year-old male patient with diabetes known since 12 years. Numerous microaneurysms and yellowish deposits are present as seen in figure 8a from 1963. Figure 8b gives the same area in 1968. The yellowish exudates and all microaneurysms have disappeared, even those which were not coagulated.*

pear even if not coagulated. It has been shown that diabetic retinopathy may be prevented or regressed by the presence or occurrence of high myopia, optical atrophy, disseminated chorioiditis or by extensive diathermy scars (*8*, *9*, *14–18*). It could be concluded that the effect of photocoagulation is due to the destruction of retinal tissue by which oxygen supply of the remaining retina becomes better. Amalric has proposed this hypothesis a few years ago (*15*).

Photocoagulation is certainly a destructive and symptomatic treatment of diabetic retinopathy. As the risk of this treatment is low when performed in early stages, we recommend early treatment of diabetic retinopathy with photocoagulation.



FIGURES 9a–c.—*Case 4: 22-year-old female patient with diabetes known since 7 years, right eye. Figure 9a shows the fundus before treatment. We call this type of severe juvenile diabetic retinopathy rubcosis retinae. All neoformations of vessels lie in the level of the retina with multiple hemorrhages, retinal edema. Figure 9a was taken in 1964, figure 9b 2 months after the coagulation. The regression of the symptoms of diabetic retinopathy is rather quick. The choroidal pattern is much better visible, because the retinal edema has decreased. A great part of the new formed vessels have disappeared. Some yellowish deposits are still visible in the center. Figure 9c gives the same area 3 years later with further improvement in spite of the fact that no further treatment has been performed.*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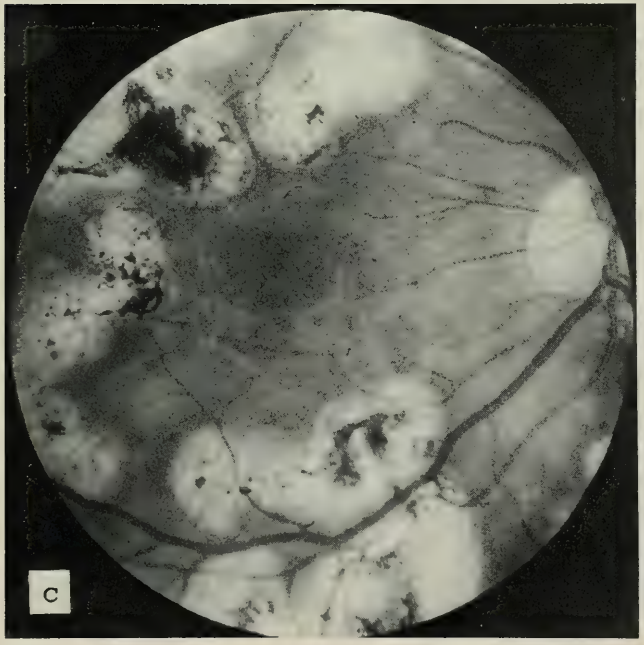
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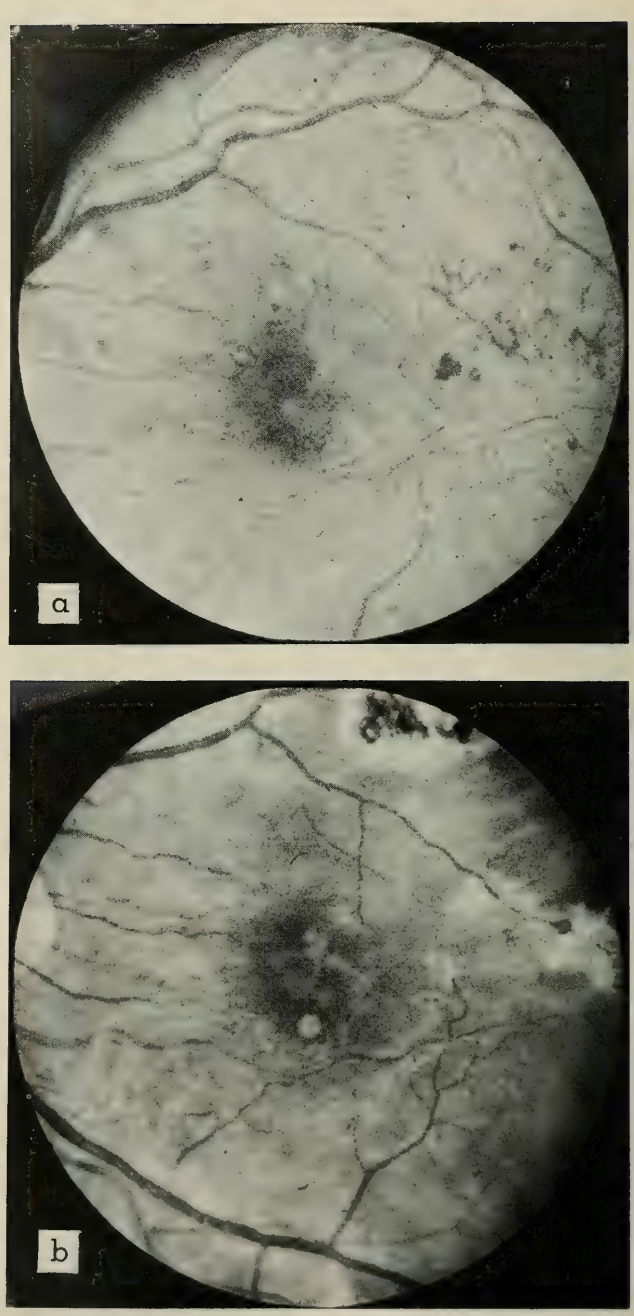
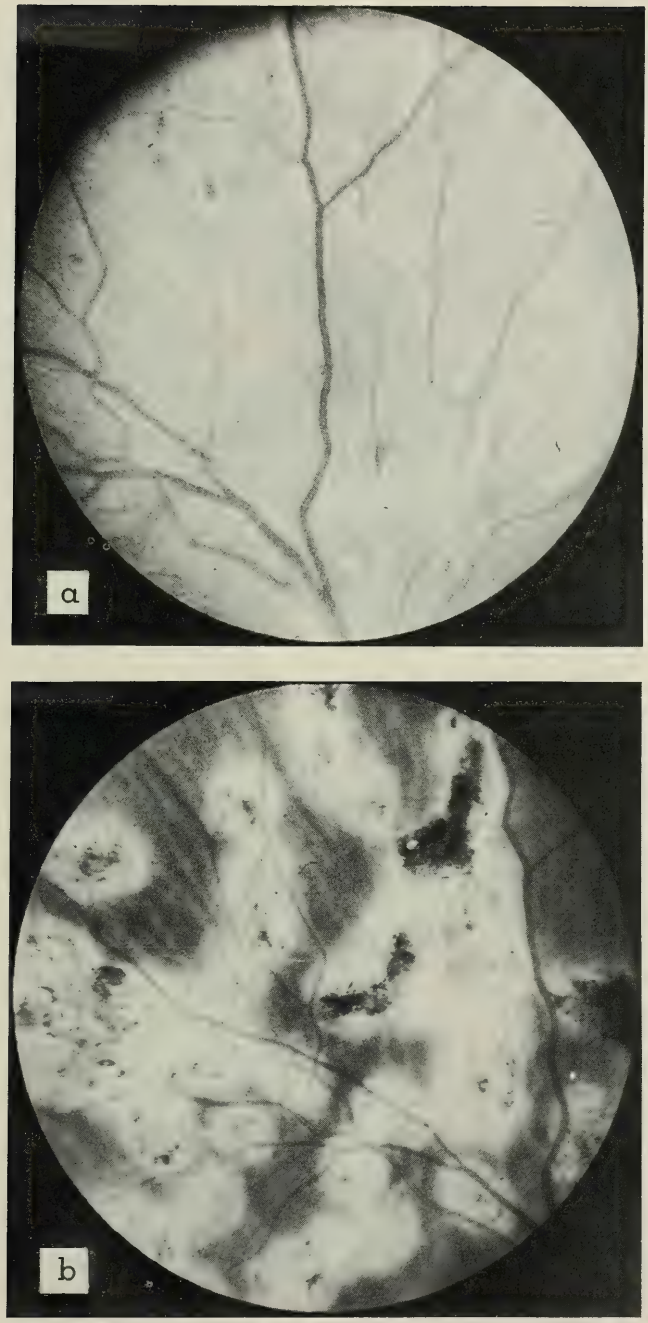
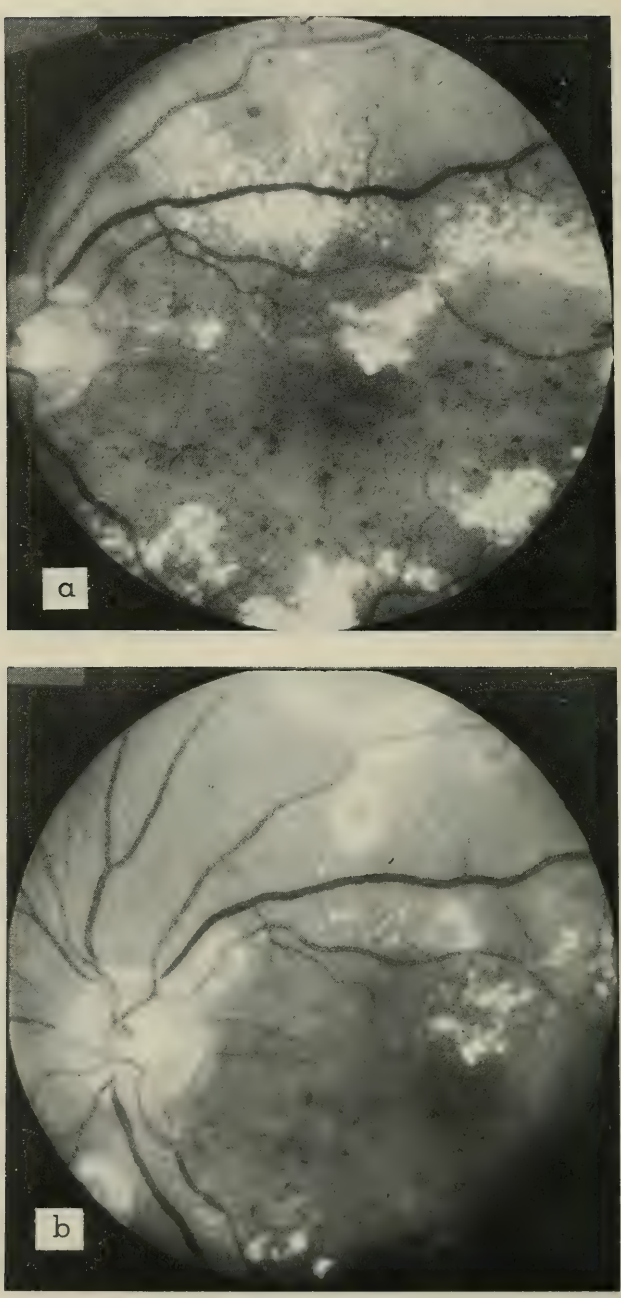


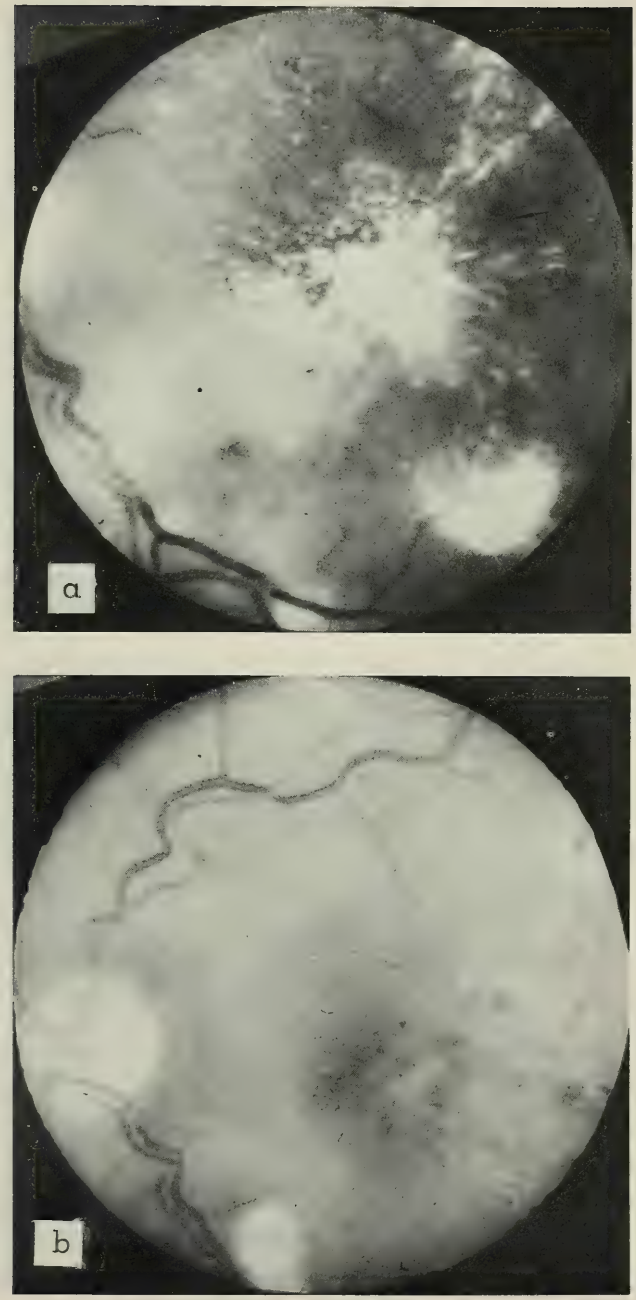
FIGURES 10a–b.—*Case 5: Same as case 4, left eye. Figure 10a, before treatment, 10b, 4 years after photocoagulation. In spite of the fact that this eye was treated with fewer coagulations as the fellow eye and with greater distance from the macula the decrease of symptoms has been the same as in the fellow eye.*



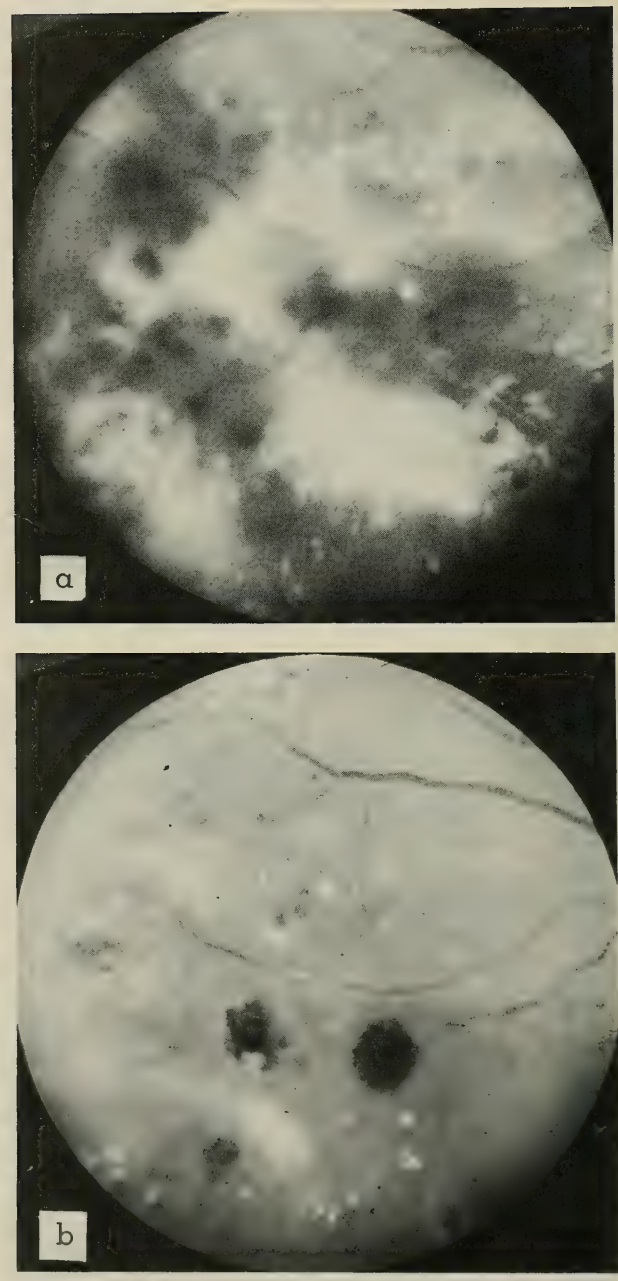
FIGURES 11a–b.—*Case 6: 23-year-old female patient with diabetes known since 7 years. This time we show a peripheral area with changes similar to the previous case. In figure 11a neoformations and hemorrhages can be seen at the level of the retina. After a rather excessive photocoagulation, all these changes had disappeared as shown in figure 11b which was taken 3 years later.*



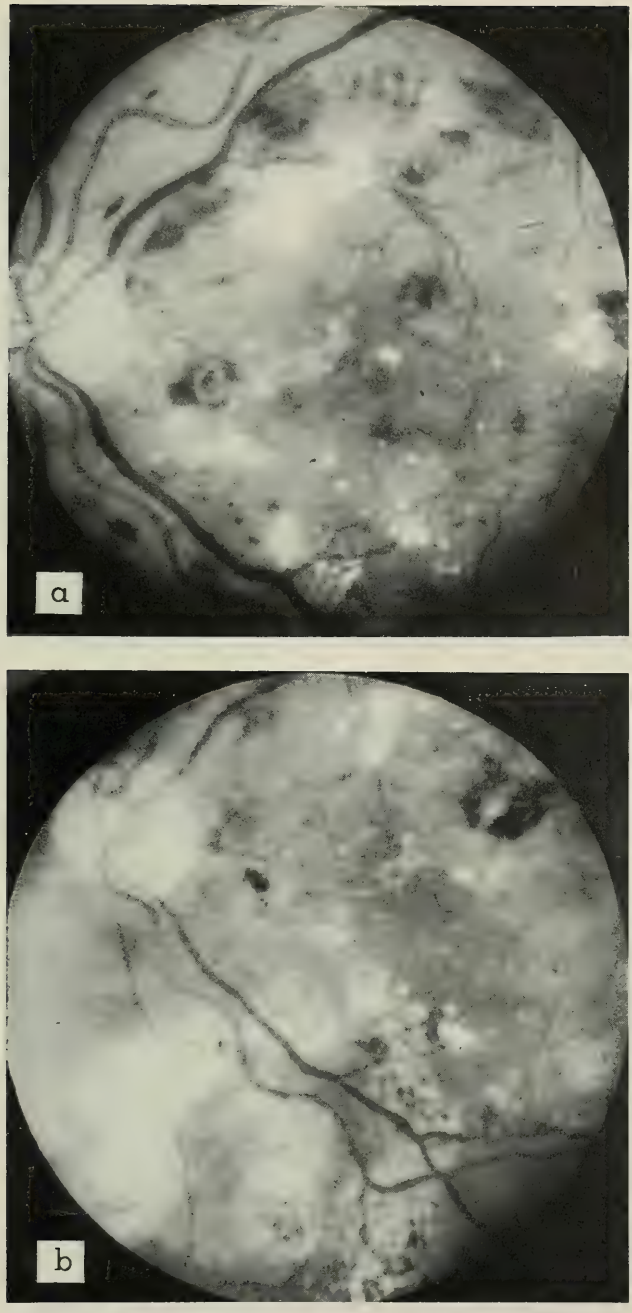
FIGURES 12a–b.—*Case 7: 62-year-old male patient with diabetes known since 11 years. Between figures 12 a and b there is an interval of 1 year. There is a marked regression of yellowish deposits. No further treatment is performed as we expect further regression of all the symptoms.*



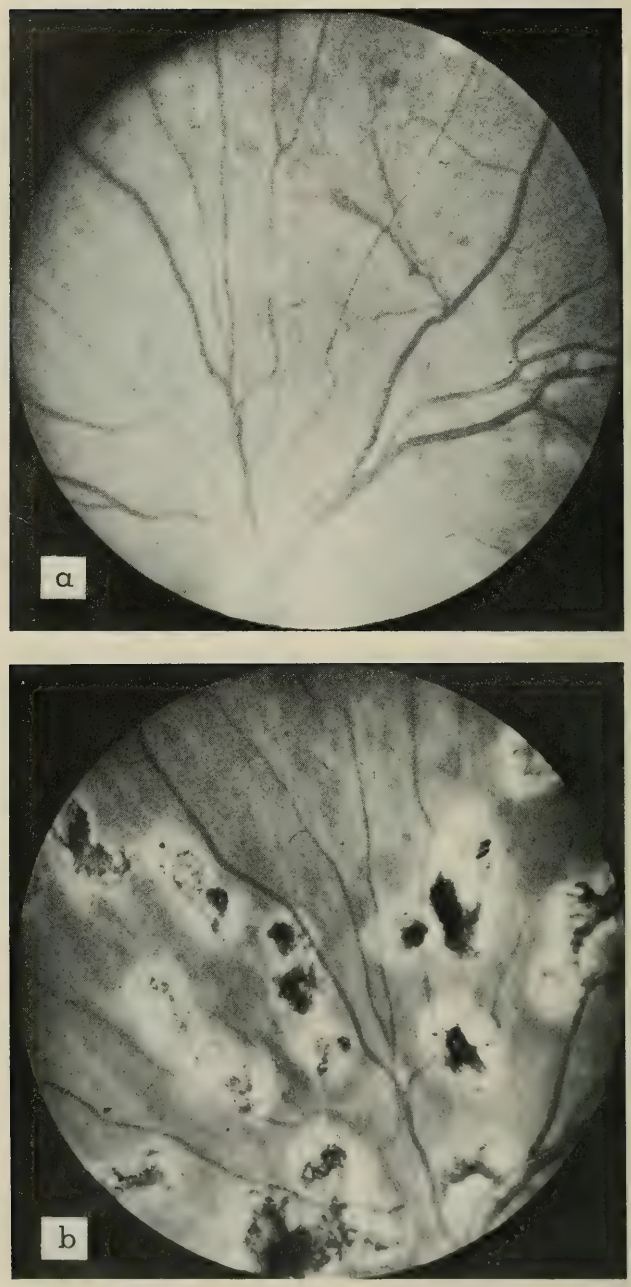
FIGURES 13a–b.—*Case 8: 60-year-old female patient with diabetes known since 10 years. Between figures 13 a and b is an interval of 3 years. Marked decrease of yellowish exudates in spite of the fact that multiple microaneurysms are still visible in the macular area. In this case also the coagulations are located rather far away from the macula and disc.*



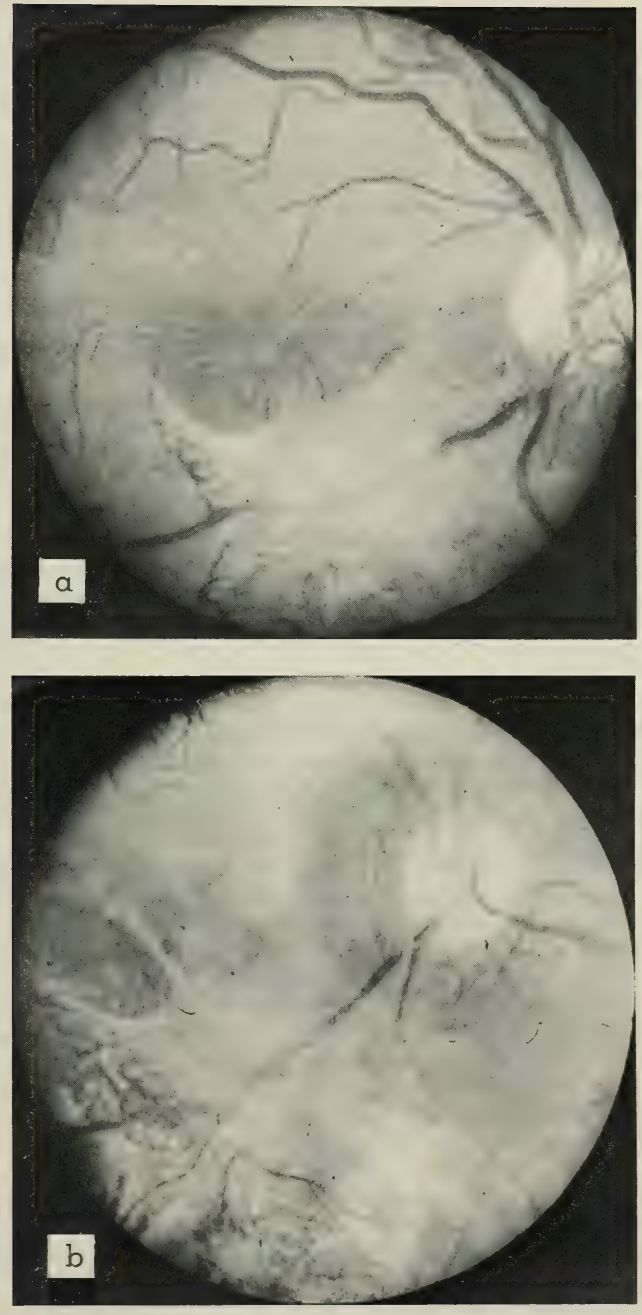
FIGURES 14a–b.—*Case 9: 66-year-old female patient with diabetes known since 2 years. Figure 14a presents a retinopathy with excessive yellowish deposits and retinal edema in addition to microaneurysms and hemorrhages. One year later the yellowish deposits have decreased tremendously and the retinal pattern becomes better visible. Further improvement can be expected.*



FIGURES 15a–b.—*Case 10: 54-year-old male patient with diabetes known for 13 years. In figure 15a we see a severe diabetic retinopathy with severe edema of the retina and several hemorrhages. Figure 15b is taken 8 months later and shows a marked decrease of the retinal edema and the yellowish exudates. Further improvement can be expected.*



FIGURES 16a–b.—*Case 11: 22-year-old female patient with diabetes known for 10 years. Figure 16a demonstrates neovascularization at the level of the retina plus beginning proliferation into the vitreous. Figure 16b, taken 2 years later, shows that the proliferation has disappeared and new proliferations did not occur.*



FIGURES 17a–b.—*Case 12: 30-year-old female patient with diabetes known since 21 years. The patient came, as one can see from figure 17a, with extensive proliferations into the vitreous. In spite of several photocoagulations, the proliferation progressed and new proliferations occurred around the disc. Some of the old coagulations are covered with a rete mirabilis of new-formed vessels.*

SUMMARY

The early symptoms of diabetic retinopathy are reversible when photocoagulation is performed in small disseminated foci over the affected areas. By treating the early stages, the late stages with proliferations, hemorrhages and retinal detachment can be prevented. In cases of prolifertive diabetic retinopathy, photocoagulation can be applied; but the number of complications is greater, and the beneficial effect is doubtful.

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CHAPTER 49

A Review of 232 Patients Including 401 Eyes With Diabetic Retinopathy Treated by Light Coagulation[1]

PAUL C. WETZIG, M.D.
C. NEAL JEPSON, M.D.

INTRODUCTION

There is no cure for diabetes mellitus. It, therefore, remains the responsibility of the ophthalmologist to forestall the progression of the ocular complication of proliferative diabetic retinopathy by other means, if vision is to be preserved.

For the past 9 years it has become increasingly more apparent in our experience and in the experience of others that light coagulation can rapidly alter the course of proliferative diabetic retinopathy. We have observed that light coagulation may bring about a "remission" of the disease process in some cases (*1*). This has been manifested chiefly by an alteration in the appearance of the vascular pattern in the eye. The most striking, consistent finding is a diminution in venous congestion and the disappearance of retinal edema. Aneurysms and exudates tend to disappear at a later date.

The purpose of this paper is to share our experiences with other investigators. In so doing we hope to be able to improve upon the results for preserving vision which this mode of therapy offers. We should be able to accomplish this end by achieving a better selection of patients for treatment dependent upon the use of a standardized classification of diabetic retinopathy, thereby allowing treatment in earlier stages of the disease and by improvement of the techniques and equipment employed.

METHOD

Light coagulation is usually carried out under local anesthesia and carries minimal hazards; because of this, a poor general health status does not necessarily contraindicate treatment. Photocoagulation may be done whenever the local eye condition would indicate that treatment is indicated. The technique used is essentially the same as reported

[1] See appendix N for raw data on individual patients.

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in our previous writings and those of others (*1–5*). The injection of sodium fluorescein into the venous circulation has not only proved to be of importance in documenting the circulation pattern in the eye by photography, but also is an adjunct in treatment. The circulatory defect can be determined by the green discoloration in the eye. We have found that the green color enhances the absorption of heat from relatively nonpigmented structures, thus aiding in their destruction. The fluorescein may also act as a protective shield, preserving the underlying structures. We have utilized the Zeiss photocoagulator.

Our method is as follows: the pupil is widely dilated and the eye is then immobilized and anesthetized by the injection of retrobulbar anesthesia. Examination through the photocoagulator is commenced and treatment is subsequently instituted. In general the treatment routine begins at the disc and the vascular patterns of the major vascular arcades are followed, beginning on the nasal side of the disc. All abnormal structures which can be visualized are obliterated. This is usually achieved by the use of the 6° aperture, and the intensity of the burn is regulated so that a mild yellow burn is obtained. The treatment is directed primarily at the sites where the green discoloration of the fluorescein is noted. The treatment areas are, as a rule, not made conconfluent; but areas of tissue are spared between the applications, thus reducing disturbances in the visual field. All abnormal structures are treated including retinal new-vessel formation, intravitreous retinitis proliferans, microaneurysms, and bleeding sites. Those structures which are approximated to the pigment epithelium offer no problem for complete destruction. Fibrovascular fans projecting into the vitreous are less easily burned. However, with the use of the intravenous fluorescein technique such structures are more easily destroyed in most cases.

Detachment of the retina may be delimited in some cases; however, in others the detachment may be progressive and when markedly so, may produce holes in the retina at the site of previously applied light coagulation. The course of the retinal detachment is uncertain. Sometimes when the detachment is nonrhegmatogenous, the retina may spontaneously settle back. If this does not occur and holes are visualized then the conventional methods of retinal detachment surgery are in order. Over treatment should be avoided. There is little inconvenience and danger from treatment and, therefore, it is better to repeat treatment as deemed necessary. As many as 75 to 100 applications may be given in the first therapeutic session. Additional treatment may be necessary in 3 to 6 months if the disease appears to be progressing. Treatment is thought to be adequate when signs of remission occur, as indicated by diminution of venous congestion and disappearance of

retinal edema. If the remission progresses the aneurysms and exudates will gradually disappear, and fibrovascular membranes which project into the vitreous tend to become avascular.

One of the major causes of failure in our early cases has been a progression of the retinopathy in the region of the optic disc and the macula, which are common sites of involvement in the disease. There has been a natural reluctance by most operators to attempt to destroy tissue in these regions for fear of further damaging these vital structures. We have found that with the use of the intravenous fluorescein technique and caution in the use of the light coagulator that the abnormal structures on the optic disc may be destroyed without reduction of vision or sector field loss. When these abnormal structures are seen in their early stages they are easily destroyed. However, if the new growth is extensive and projects into the vitreous very far anteriorly, it is more difficult to destroy and the hazards are greater. In some cases these structures, while reduced in size and vascularity, persist as vascular fronds projecting into the vitreous and may subsequently hemorrhage into the vitreous. If, however, the disease process appears to be going into a general stage of remission, these vascular channels may also occlude, leaving an avascular frond projecting into the vitreous. This is not a rapid occurrence but may require an interval of 3 to 6 months to occur. When there are hard exudates in the retina a scotoma may be demonstrated by use of the visuscope. If the exudates disappear following treatment, the scotoma also disappears when the exudates lie in the extramacular regions. When these exudates occur in the fovea, central vision does not return after their disappearence, although there may be a subjective improvement in vision from clearing of the extrafoveal structures. When treating in the macular area the $1\frac{1}{2}°$ aperture of the light coagulator is used and the treatment is directed to the small vessels which appear to be leading into the area of aneurysms and exudates. The fovea itself is scrupulously avoided. Abnormalities in the papillomacular area itself may be treated without production of a loss in central visual acuity.

RESULTS

Results of the treatment are still difficult to evaluate. However, with a greater number of patients treated and with a longer term of followup more positive conclusions may be drawn. Two hundred and thirty-two patients including 401 eyes have been treated. Twenty-five patients including 38 eyes have been lost to followup. Total length of followup time is 101 months. The average followup time per eye is 20 months.

The eyes have been classified according to the O'Hara Classification [1]. Patients lost to followup and those in the H_2 category at the beginning of treatment have been excluded in the evaluation. The visual retention index has been achieved by dividing the months of followup into the total number of months during which vision was retained. To further simplify the classification the total number has been divided into two groups. In the first group are the B, N_1, and F_1 classification. The second group includes the N_2 and F_2 classifications. This would roughly divide the series into two groups, the first including early to moderately advanced cases and the second representing the more far advanced cases. The visual retention index in the first group has been 0.96 and in the second, 0.65. Complications in group 1 have been zero and complications in group 2 have been 21. We recognize many inherent inadequacies in this oversimplified classification, but we have been able to draw some positive conclusions.

In reviewing the 232 patients followed, it is quite obvious to us that the earlier in the disease process that light-coagulation treatment has been instituted the more favorable the results will be. This is borne out expecially in the long-term followups.

With the use of fluorescein angiography we have observed that the disease process is often far more advanced than the original examination with conventional methods indicated. The earliest signs appear to be a slowing in the circulation time on the venous side. This has been observed in an eye in which certain sectors of the venous circulation will empty of dye in a normal manner whereas in other channels there appears to be a slowing of the emptying time (figs. 1–4). When this slowing occurs there may be actually a leakage of the dye from the major veins. As this stasis persists new vessel formation is noted in these areas. It is our feeling that treatment should be initiated when the early signs of the disease are seen as represented by the abnormalities demonstrated by fluorescence angiography.

The majority of patients, however, are not seen in the early stages of the disease. Since we are obliged to preserve vision in all patients, different techniques must be applied in the more advanced cases. The results have obviously not been as good in these more advanced cases, and the complications of treatment have been more frequent. In an analysis of the cause of our failures, it becomes obvious that in the more advanced stages of the disease the prognosis is less good for any form of treatment, especially when the optic nerve and the macula are extensively involved. We feel that in the later stages the vitreous begins to play an important role in the progression of the disease. Progression of the retinopathy manifests itself by further hemorrhage

[1] O'Hare Classification, p. xxi.

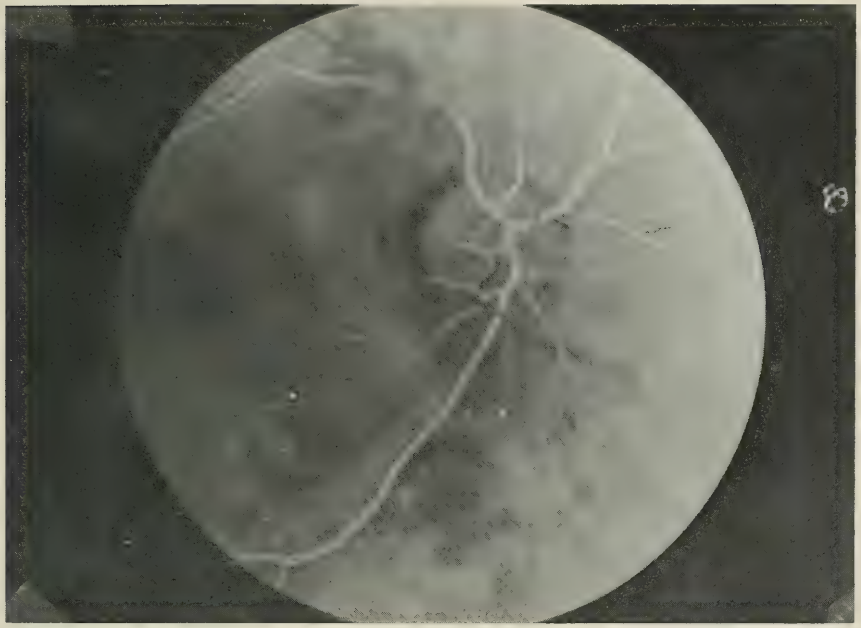

FIGURE 1.—*Early arterial phase (15 seconds after fluorescein injection). No fluorescein leakage seen.*

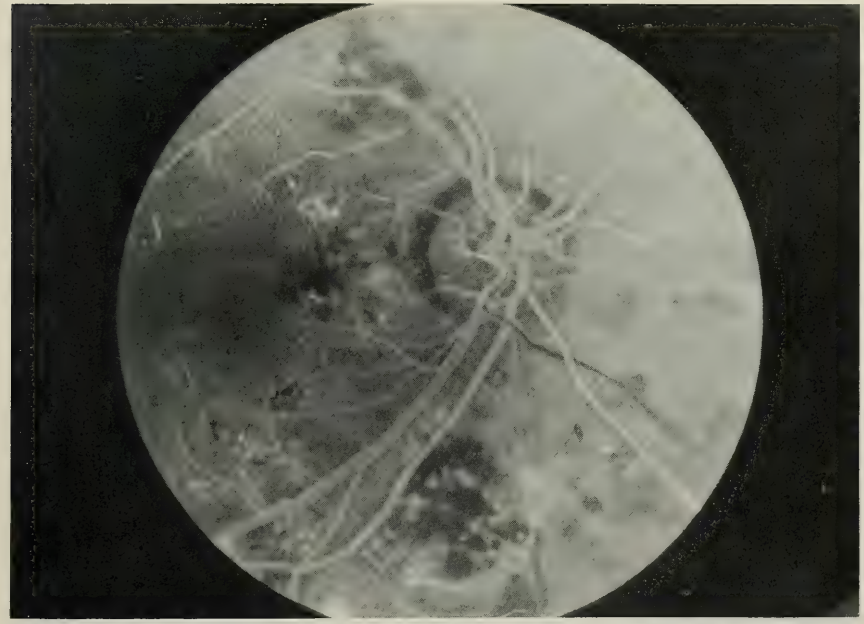

FIGURE 2.—*Early arterio-venous phase (25 seconds after injection) demonstrates minimal peri-vascular venous leakage, venous stasis and many abnormal capillary shunts with microaneurysms.*

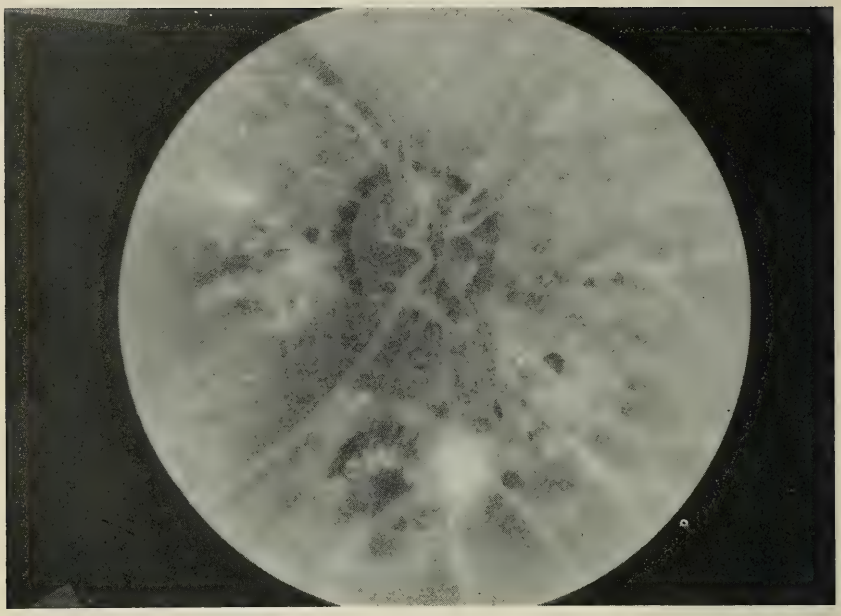

FIGURE 3.—*Late arterio-venous phase (35 seconds after injection) demonstrates marked fluorescein leakage from vein at 6 o'clock and also venous stasis in veins at 3 o'clock.*

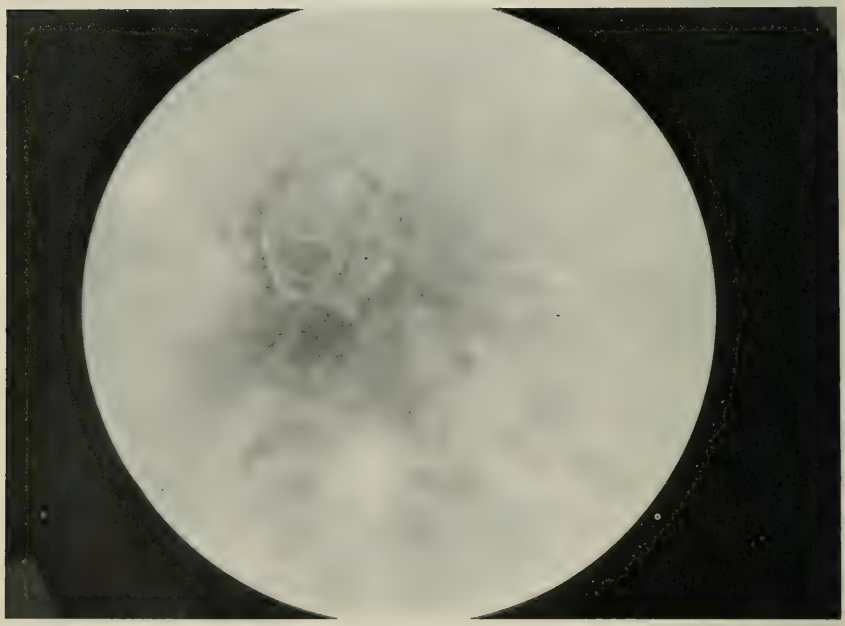

FIGURE 4.—*Post venous phase (2 minutes after injection) indicates marked general leakage from major venous channels.*

into the vitreous, further growth of the retinitis proliferans into the macular region and progressive detaching of the retina. Secondary factors in the production of visual loss are cataracts, rubeosis of the iris with associated glaucoma and macular degeneration. These complications are not felt to be indications of failure of treatment or complications of the treatment but rather a natural progression of the condition.

COMPLICATIONS

The major complication encountered has been detaching of the retina. In many cases this has occurred when detachment has preexisted the treatment and attempts have been made to delimit the detachment. These cases have been included because it has been felt that the treatment may have aggravated the speed of the detachment. When this has occurred within a period of 3 weeks following treatment we have listed it as a complication.

Hemorrhaging into the vitreous has been the second most common complication. This has been observed at the time of treatment whereupon more therapy is applied to the bleeding sites and sometimes the bleeding has been stopped. We have also observed that bleeding may occur following the installation of the retrobulbar anesthesia. The mechanism of this is felt to be an alteration in the ocular pressure, in which the balance between the abnormal vessels and intraocular pressure has been disturbed. When this hemorrhaging has occurred into the retina or into the vitreous within 1 week following therapy we have listed it as a complication. Macular burns have occurred in three cases. These are technical errors and should be avoided. They may be encountered more frequently when the eye is incompletely immobolized and treatment is attempted in the paramacular region. It is also more likely to occur when the media are hazy and when the macular structures have been distorted by new-vessel formation. Complications of the anterior segment have also been encountered and these are more common in patients whose pupils will not dilate widely. When there is an inadequate dilitation of the pupil, greater intensity of light is usually required to produce an adequate burn in the retina. Therefore, complications in the anterior segment are more likely to occur, probably as a result of an absorption of heat by the iris. These are manifested by an iritis often associated with a keratitis. The keratitis thus produced has always cleared without permanent corneal opacification. Iris atrophy and associated posterior synechia are then seen. The anterior lens capsule underlying these structures may also be involved

with opacification occurring. However these opacities are not progressive and when peripheral do not produce visual loss. There has been one branch vein occlusion.

COMMENT

The mechanism of the action of light-coagulation therapy is unknown. Our observations of the circulation of fluorescein in the retinal circulation have led us to some theoretical conclusions. It may be that there is an overall reduction of blood supply in the retina, which is brought about by the destruction of the smaller vessels which normally lead into the main venous channels. This would lead to a reversal of the cycle of congestion, edema, exudation, hemmorrhage, and new-vessel formation. This is dramatically seen in the first 2 weeks following light-coagulation therapy. Another possible mechanism would be in the alteration of the metabolic needs of the retina, wherein requirements for new-vessel formation have been eliminated. Freeing of vitreous traction upon the retina and retinal vessels may be another possible mechanism.

CONCLUSION

In conclusion, the argument may be developed that blindness from proliferative diabetic retinopathy is due to hemmorrhage into the retina and vitreous, exudation and edema in the retina, the growth of proliferative tissue into the retina, vitreous, and retinal detachment. These processes may be halted or reversed by light-coagulation therapy. Therefore, this form of treatment must be presumed to be of some value in preserving vision. It appears that it is now our present responsibility to improve upon our techniques to increase the good results in this approach until a cure for the generalized disease can be found.

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CHAPTER 50

The Treatment of Diabetic Retinopathy by Laser Photocoagulation

H. CHRISTIAN ZWENG, M.D.

The usefulness of laser photocoagulation in the treatment of diabetic retinopathy is, at this writing, uncertain.

CATEGORIES OF PATIENTS AND RATIONALE OF TREATMENT

We have used presently available laser photocoagulators in the treatment of diabetic retinopathy in the following three classifications of patients:

(1) Patients with grade 1 to 2 diabetic retinopathy demonstrating microaneurysms, fine neovascular tufts with areas extending in diameter no larger than 500 microns, and small hemorrhagic areas of approximately the same size at the largest;

The rationale for treatment of these patients is as follows: Fluorescein retinal angiography pinpoints leakage from micoaneurysms and from the sites of small hemorrhages. Laser photocoagulation is able to seal these off, hopefully interrupting the events that lead to vitreous change. The neovascular tufts are thin-walled vessels prone to hemorrhage; the obliteration of these is, therefore, useful prophylaxis.

(2) Patients with microcystic edema of the macula in whom relatively discrete fluorescein leaks are demonstrable;

The rationale for treatment of these patients is that laser photocoagulation can seal off vascular leaks in the macula with a minimum of trauma, leading to absorption of the macular fluid with resulting improvement in vision.

(3) Patients with retinitis proliferans in whom there are obvious retinal traction folds at the base of the vitreal strands;

Placement of laser photocoagulation lesions around the base of such strands is done to offer the resistance of chorioretinitic scars to the pulling action of such strands.

Palo Alto Medical Clinic, Palo Alto, Calif.

EXPERIENCE TO DATE

Category 1

In the last 3 years, 22 patients have been admitted to treatment who fit the following criteria:

(*a*) No more than grade 1 or grade 2 changes in both retinae.

(*b*) Agreement to treat only the eye that initially appears worse, leaving the better eye as a control.

(*c*) Agreement to be seen every month indefinitely.

To date four untreated eyes have developed at least grade 3 changes with large retinal or vitreal hemorrhages while none of the treated eyes has developed such changes.

Category 2

Eight eyes treated: In four there has been clearing of edema and leakage of fluorescein and substantial improvement in vision (to at least 20/30 from 20/100). In four no improvement in vision occurred, no subsidence of edema was seen and no decrease in fluorescein leakage photographed.

Category 3

Eight eyes treated: None has gone on to retinal tears.

In addition, 55 eyes have been treated with grade 3 or grade 4 changes. Treatment was as described in category 1, but no controls were set up as in category 1. In none of these was the retinopathy favorably influenced.

POSSIBLE FUTURE TREATMENT

All present available laser photocoagulators use the ruby as the lasing material. This gives a beam output of 6,943 angstroms in the deep red. This wavelength is absorbed by hemoglobin by only about 5 percent. Obviously, this makes the treatment of hemorrhage and aberrant blood vessels difficult. However, such photocoagulation is possible by two mechanisms: first, by the proliferation of pigment in the retina as a result of a first exposure with final coagulation taking place a week or two later; and second, because the 5-percent absorption is enough to effect photocoagulation initially in some instances.

Obviously the use of a wavelength that is better absorbed by hemoglobin than 6,943 angstroms seems desirable. The argon continuous-wave laser emits its two main wavelengths in the blue-green part of the spectrum, 4,880 angstroms and 5,145 angstroms. In experimental studies this laser has demonstrated the capability of occluding both retinal arteries and retinal veins. Clinical trials are now beginning in patients with diabetic retionpathy and will be reported on soon. With this capability at hand, a very selective job can be done on aberrant blood vessels, hopefully cutting down on the hemorrhages and exudates of diabetic retinopathy.

Therefore, present-day laser photocoagulation may be useful in diabetic retinopathy, but certainly only in grade 1 and grade 2 retinae, in some cases of macular microcystic edema and perhaps to help prevent retinal tears. Argon laser photocoagulation perhaps will extend the usage of photocoagulation in diabetic retinopathy.

CHAPTER 51

Summary of Visual and Anatomic Results From Papers on Photocoagulation

BRADLEY R. STRAATSMA, M.D.

Since 1955, when photocoagulation was first employed in the treatment for diabetic retinopathy, interest in this method of therapy has steadily increased (*1*). Indicative of this, material incorporated in this symposium includes 16 papers that discuss various aspects of this treatment modality.

To appreciate fully the valuable information contained in this material, each paper must be reviewed individually. There is a wide range of theoretical analysis and clinical practice, but, of greater importance, are major areas of agreement. To summarize important aspects, consideration will be given to treatment rationale, results, and complications.

RATIONALE

The rationale for photocoagulation therapy stems from current concepts of the pathogenesis of diabetic retinopathy. These concepts view diabetic retinopathy as a syndrome that is related to progressive retinal ischemia, and, in its full sequence, is characterized by nonproliferative (or background) and proliferative changes. Included in the former are microaneurysms, retinal hemorrhages, soft exudates, hard exudates, and irregularities in retinal veins and other retinal vessels. Typical of proliferative retinopathy are neovascularization, fibrous tissue proliferation, subhyaloid and vitreous hemorrhage, traction-induced retinoschisis, and retinal detachment. During the course of this retinopathy, vision impairment may result from macular disease, subhyaloid and vitreous hemorrhage, or retinal detachment.

To cope with this varied but generally progressive retinopathy, retinal photocoagulation is employed, according to various authors, in an effort to—

(1) Coagulate and destroy areas of circulatory imbalance responsible for retinal edema and exudates;

(2) Coagulate areas with ischemia of critical degree and prevent stimulation of proliferation;

(3) Coagulate new vessels to eliminate sources of potential viterous hemorrhage and prevent extension of retinovitreal adhesions;

(4) Coagulate bleeding sites responsible for subhyaloid and vitreous hemorrhage;

(5) Form chorioretinal adhesions to prevent or delimit retinal detachment; and

(6) Destroy retinal tissue and reduce the overall metabolic requirement and vascular activity of the retina so that progression of nonproliferative and proliferative disease is prevented.

RESULTS

These reasons for treatment are quite varied, but, interestingly, coagulation performed for different reasons and by different techniques may, as recognized by a number of authors, achieve a very similar end result. For example, extensive treatment to coagulate new vessels and eliminate the sources of potential vitreous hemorrhage may destroy an extensive amount of retinal tissue and reduce the overall metabolic requirement of the retina. This similarity adds significance to an appraisal of the overall results of photocoagulation therapy.

As a basis for this appraisal, the results of photocoagulation applied to nearly 1,800 eyes with diabetic retinopathy are recorded in the papers of this symposium (chs. 35–43, 46–50). In general, these papers demonstrate that in some patients, for at least a limited period of time, it is possible to ameliorate the signs and symptoms of diabetic retinopathy. Various authors note that retinal photocoagulation may decrease or, in some instances, eliminate—

(1) Retinal microaneurysms, hemorrhages, and exudates;

(2) Retinal edema;

(3) General retinal congestion;

(4) Retinal neovascularization;

(5) The vascular component of retinitis proliferans; and may

(6) Prevent or demarcate some types of retinal detachment.

For more precise evaluation of the results of therapy, it is necessary to consider separately nonproliferative and proliferative retinopathy. Moreover, for each category, it is necessary to compare the results in treated eyes with the results in control eyes and with information regarding the natural course of diabetic retinopathy.

The results of treatment of nonproliferative retinopathy are reported in four papers that cite experience with 159 eyes (table 1):

TABLE 1.—*Nonproliferative Retinopathy*

	Eyes
Wessing and Meyer-Schwickerath (ch. 48)	129
Cleasby[1] (ch. 36)	14
Welch[1] (ch. 47)	8
Zweng[1] (ch. 50)	8
Total	159

[1] The precise type of retinopathy in these eyes was not specified, but only nonproliferative changes were described and treated.

Of special interest, Wessing and Meyer-Schwickerath describe 49 eyes with nonproliferative retinopathy and good vision that were observed for at least 9 months, and in many instances more than 3 years, after treatment. They report complete regression of the retinopathy in 19, improvement in 25, and progression of the disease in five eyes. Vision in these eyes with nonproliferative disease was generally unchanged by treatment.

Other cases, in which only nonproliferative changes were described and treated, presented retinopathy that was associated with macular edema, exudates and impaired vision (chs. 36, 47, 50). In this category, Welch photocoagulated eight eyes and reported an improvement of vision in six eyes.

These studies of photocoagulation for nonproliferative diabetic retinopathy with good vision do not present controlled observations on treated and untreated eyes. Moreover, when the number of treated cases and the period of followup is compared with Caird's study of the natural history of nonproliferative retinopathy over a 5-year period, it is evident that no conclusion regarding the role of photocoagulation in nonproliferative diabetic retinopathy associated with good vision is warranted at this time (ch. 3). Also in need of further long-term and controlled documentation is the role of photocoagulation in nonproliferative retinopathy associated with impaired vision. However, the improvement in vision following photocoagulation of eyes in this category contrasts with the generally downhill course of vision in eyes with this clinical picture (ch. 3), and, therefore, the results of photocoagulation for nonproliferative retinopathy with impaired vision are particularly encouraging.

The treatment of proliferative retinopathy is reported in 13 papers that cite experience with 1,635 eyes (table 2):

TABLE 2.—*Proliferative retinopathy*

	Eyes
Aiello, Beetham, et al. (ch. 35)	218
Cleasby (ch. 36)	87
Dobree (ch. 37)	60
Harris (ch. 38)	41
Larsen (ch. 39)	46
McMeel and Van Heuven (ch. 40)	100
Mortimer (ch. 41)	108
Okun and Johnston (ch. 42)	359
Roth and Rand (ch. 43)	46
Welch (ch. 47)	[1] 24
Wessing and Meyer-Schwickerath (ch. 48)	60
Wetzig and Jepson (ch. 49)	401
Zweng (ch. 50)	85
Total	1,635

[1] The report cites 24 cases.

A number of authors note that anatomical and visual results following treatment of relatively early proliferative retinopathy were better than results following treatment of late stages of proliferative retinopathy (chs. 35, 42, 49). Vision varied following treatment but generally deteriorated in accordance with progression of the retinopathy. After extensive treatment, the field of vision was generally somewhat restricted, but patients were not usually aware of a field defect, and nerve fiber bundle defects were only occasionally detected.

Illustrative of the general response following photocoagulation of proliferative retinopathy is the report by Okun and Johnston (ch. 42). These authors treated 254 eyes, and noted that after a followup of from 6 to 72 months (an average followup of 28 months), 65 percent of the eyes were stabilized. Data from this study also indicated that eyes with early proliferative retinopathy at the time of treatment have a better prognosis for stabilization of the retinopathy and for preservation of vision than eyes with late stages of retinopathy.

For critical evaluation of the results of photocoagulation for proliferative diabetic retinopathy, Aiello et al. (ch. 35), Okum and Johnston (ch. 42), and Zweng (ch. 50) treated one eye in a series of patients and observed the opposite eye as a control. In addition, Dobree treated a series of eyes and used a series of comparable eyes as controls (ch. 37). All of these controlled studies have demonstrated a more favorable course in eyes treated with photocoagulation. Representative of this form of controlled study is a series reported by Okun and Johnston. In 52 patients with symmetrical proliferative retinopathy, one eye was treated and the opposite eye was observed. After a followup period of from 5 to 52 months (an average followup of 29 months), the treated eye was better in 23 cases, equal to the untreated eye in 28 cases and worse than the untreated eye in one case.

Comparing the results of photocoagulation with the natural history of the disease, it is evident that the photocoagulated eyes demonstrate a percentage of stabilization higher than that noted by Beetham in his study of the natural history of proliferative diabetic retinopathy (*2*). Therefore, on the basis of controlled studies and a comparison of treated eyes with the natural history of the disease, it may be concluded that photocoagulation is an effective treatment for proliferative diabetic retinopathy. In some instances, it is capable of arresting or retarding progression of the retinopathy.

COMPLICATIONS

Though this conclusion is gratifying, it is clear that photocoagulation is not able to prevent loss of vision in a number of eyes and blind-

ness in a number of diabetic patients. These failures are due in part to the limitations of treatment and in part to complications associated with therapy. Though the incidence of adverse effects is not known, and there is no unanimity regarding retrograde changes that are related to treatment, complications ascribed to photocoagulation include—

(1) Vitreous hemorrhage, membrane formation, and fibrosis;

(2) Retinal detachment, hemorrhage, vascular occlusion, and tear;

(3) Macular edema, exudate, hemorrhage, and accidental photocoagulation;

(4) Optic atrophy, cataract, rubeosis iridis, and absolute glaucoma; and

(5) Loss of vision, arcuate scotoma, and visual field defect.

In conclusion, photocoagulation of diabetic retinopathy is increasing. This therapy is designed to coagulate areas of circulatory imbalance, destroy new vessels, and reduce the overall metabolic requirements of the retina.

Photocoagulation of 159 eyes with nonproliferative retinopathy is reported, but no conclusion regarding the effectiveness of this treatment in eyes with nonproliferative retinopathy and good vision is warranted at this time. In eyes with nonproliferative retinopathy and impaired vision, photocoagulation is sometimes followed by an improvement in visual acuity. Although no conclusion can be made at this time, results of treatment for this category are encouraging.

Photocoagulation of 1,635 eyes with proliferative retinopathy is reported. Based on controlled studies and a comparison of treated eyes with the natural history of the disease, photocoagulation is an effective treatment that, in some instances, is capable of arresting or retarding the progression of diabetic retinopathy.

Associated with photocoagulation for proliferative retinopathy, complications include vitreous hemorrhage, retinal detachment, and other adverse effects. While there is an urgent need for better methods to prevent and control diabetic retinopathy, photocoagulation currently occupies a place in the management of this important disease.

References

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Discussion of Visual and Anatomic Results of Photocoagulation

IRVING LEOPOLD, M.D., *Moderator*

Dr. Leopold: Dr. Wessing, you and Dr. Meyer-Schwickerath were, if not the first, among the first to ever use this technique in diabetic retinopathy. What was it that stimulated you to undertake such an approach?

Dr. Wessing: The first intention was to prevent hemorrhages from new formed vessels and from microaneurysms. Also, several cases with macular lipid had extramacular coagulation, and the lipid disappeared.

Dr. Leopold: Do you have any slides of patients followed for the same period showing the same thing without photocoagulation?

Dr. Wessing: No.

Dr. Leopold: Do you have some patients like that?

Dr. Wessing: Yes.

Dr. Kohner: You reported that you had 19 patients in whom there was complete remission of retinopathy. First of all, did you have any fluorescein evidence of this? Secondly, is it possible that you destroyed so much of the retina that there wasn't anything left where there could have been retinopathy, other than, perhaps, the macula?

Another question I would like to ask is: With macular exudates, what was the visual acuity before and after coagulation? I can show you patients in whom we do nothing, but get the same result. Once the exudate is there, there is a field defect or a visual acuity defect, depending on where it is, and that doesn't improve.

Dr. Wessing: To your first question, we studied coagulation 8 years ago, and we haven't had any angiography. To the other point, the visual acuity after photocoagulation in cases with yellowish exudates is variable. We have, I think, 50 percent with impairment of the visual acuity.

Dr. Kohner: You seem to coagulate a great number of patients who only have background retinopathy. I think it's extremely important if you treat that type of patient, that you should have an adequate control series. Have you got any control series at all, or do you do one eye and not the other one?

Dr. Wessing: In the beginning we tried to coagulate only one eye in those cases who had nearly an equal retinopathy in both eyes. In the relatively advanced stages of background retinopathy, we have no series of comparison.

Dr. Lundbaek: You showed us a case with severe hard exudates in the macula, and then performed photocoagulation of other areas of the retina. The exudates disappeared. I suppose this case had poor vision before? What was the vision after?

Dr. Wessing: The vision was 1/35 before, and afterwards was 5/20.

Dr. Leopold: Dr. Beetham, in Dr. Straatsma's analysis of the results, he used your data showing the natural course of proliferative retinopathy. Have you studied any of these reports in order to correlate them personally with the progress that you would expect with and without photocoagulation?

Dr. Beetham: The series that Dr. Aiello and I are reporting has only been really underway for a year and a half. In order to make a comparison with the results which I have published of those 1,150 cases, I think you ought to have a 4- or 5-year study. So I'm unprepared to give you any figures as to comparison. We just have some impressions but no statistics.

Dr. Caird: From Dr. Beetham's data, you will see that, if the vision is going to fall below 6/15, there is roughly a 50-percent chance of that happening in 5 years in younger patients, and a 70-percent chance of that happening in 5 years in the older patients. If we consider severe deterioration with vision falling to less than 6/60, the figures are 30 percent and 40 percent respectively. It doesn't seem to me that any of the papers analyzed by Dr. Straatsma begin to reach this sort of duration of followup. I don't see that any comparison can be made, even with proliferative retinopathy. The same is true if you consider the eyes with impaired vision, in this instance meaning visual acuity between 6/24 and 6/68 inclusive. In one large group, after 5 years, approximately 50 percent had vision falling below 6/60. Again, I don't see that any of these studies go on long enough to provide a comparison. When we consider eyes with initially good vision, 6/18 or better, it would be very difficult to do better than the patients do without any treatment. In the youngest group, only 20 percent have fallen below 6/18 after 5 years, and even in the oldest group it's around 50 percent. I would be prepared to review this again in another 3 or 4 years.

Dr. Leopold: Dr. Okun in an effort to overcome this necessity of waiting for 4 or 5 years, I believe you were one of the first to start treating just one eye of selected patients who had approximately

equal retinopathy in the two eyes. I believe you picked the eye which was more severely involved to treat. I have also heard rumors that you no longer continue that study. Is that true?

Dr. Okun: This is a partial truth. In control eyes that we follow and that appear to be undergoing a rapid downhill course (and after following two of these to essentially complete blindness), we decided that we just could not do this study any longer. We had to pick a point at which we would terminate the study for the individual eye. I believe we have now treated seven of the control eyes when they have had a marked increase in the rate of progression as determined by an increase in the grade of our classification. This might be a beginning of vitreous contraction with marked hemorrhagic activity. I have the feeling that these patients will sometimes go into a phase of extremely active downhill progression and that, if not interrupted within a fairly short period of time, one can't get at these eyes again, at least with a photocoagulator, because the media become so hazy that it's not possible to photocoagulate. I have also been very much impressed (and it's very difficult to show this statistically) that photocoagulation of the bleeding site, if it can be determined at the onset of these hemorrhages, frequently will cause the bleeding site to be scarred down, and the vitreous hemorrhage to clear extremely rapidly. Thus, I felt that, for those cases that were beginning to deteriorate in this way, I could no longer hold back therapy. Those eyes which are still the same, however, continue in the control series.

What we are attempting to do in a few patients now is to treat only one eye even if we think the retinopathy is progressing fairly rapidly, but only if the retinopathy shows the earliest of changes and is symmetrical in both eyes.

Dr. McMeel: We have not worked on control patients because many of our patients were essentially uniocular when we first got to them. We had a significant number of patients who previously had pituitary ablation and/or for one reason or another were not good patients for pituitary ablation. Therefore, they had photocoagulation as an alternative procedure. Well over half of our patients were uniocular, I think.

Dr. Zweng: I think there is a sense of unease among us reflected in the questions to Dr. Wessing and to Dr. Okun, about the natural history of this disease. I think it should be put very firmly on the record that every attempt must be made by people in this field to secure comparable series using the other eye as a control. As tempting as it is for us, when we are faced with the living flesh and blood patient, to slip from the scientist to the clinician, the only way we will get the answer is to stay very firmly with the protocol, to pick the eyes that

are apparently comparable, and, if there is a choice, to treat the worst eye first and proceed in that way until death do us part. Only then, some 5 years, perhaps, from now, will we have the kind of control answers that we badly need in this field.

Dr. Keen: I was rather struck that in two of the groups the experience was very similar after treating one eye and leaving the other eye as a control. These were, in some cases at any rate, rather brisk changes in the control eye. It just occurred to me that damage produced by the coagulator might set up some sort of immune process which might damage the other retina.

Dr. Leopold: We have heard in a discussion of the advantages of hypophysectomy, that the possibility existed that adequate hypophysectomy would reduce the capillary permeability. Mr. Dobree, have you had any experience with fluorescein angiography in patients who have been photocoagulated, and does this do the same as hypophysectomy?

Mr. Dobree: No experience at all.

Dr. Leopold: Has anyone attempted to study this aspect?

Dr. Okun: No, I didn't.

Dr. McMeel: We have a few cases who have had fluorescein photos about the disc, followed by photocoagulation of the peripheral lesions. Hopefully, we will be able to get these patients back within the next few months to see whether there has been a decrease in the neovascularization pattern and leakage in the central area.

Dr. Aiello: We have done some fluorescein studies on these patients, primarily in the disc-macula area prior to photocoagulation. At first we wondered about the wisdom of this, but as time went along, we find there appears to be some improvement in the disc-macula area in the treated eyes.

Dr. Leopold: Where vessels are closed by photocoagulation, they obviously couldn't fill with blood and couldn't leak.

Dr. Aiello: Postoperatively there is little or no leakage from the disc area in some cases. These observations were made 9 months following completion of therapy, which consisted of extensive 2.5° laser photocoagulation burns (totaling approximately 600 in number) scattered in all areas except on the disc and in the macula area. Some of our fluorescein studies showed a reduction in the diffuse angiopathy, which is the term we used in the macular area, following treatment in this fashion.

Dr. Norton: I would just like to speak to the effect of photocoagulation on leakage in the retina. If the areas you destroy had leakage previously, repeat fluorescein studies at subsequent dates, as you might expect, show no leakage. However, areas that have not been

treated with photocoagulation tend to leak just as they did prior to the coagulation, at least in my observations. I don't think that photocoagulation has an effect on noncoagulated areas that are leaking. I don't want to get involved with the question of whether or not it has an effect on progression.

I do think one thing has to be emphasized. It's very important that you show photos at comparable times after the injections. You must know that a comparable dose of fluorescein is given. It's unfair to compare an arteriovenous phase or venous phase with an early arterial phase. You must see comparable stages to come to any conclusion about the leakage.

Dr. Schimek: It is interesting to comment on the change in philosophy, be it right or wrong, that is now occurring in many places in the treatment of proliferative diabetic retinopathy. From 15 years to about 4 years ago, it was always our recommendation in the severe advancing cases to consider pituitary ablation. Within the last 3 years, speaking for our own institution, there has been a much greater tendency to go first to photocoagulation. More recently my preference is very, very light laser therapy, which is repeated until we get an apparent improvement.

We have had a large group of eyes where one eye was treated similar to the way Dr. Okun described, with the other, less affected eye as the control. In practically all of these, we seem to have had a beneficial effect on the progress of the retinopathy. In a few, the other eye has had a florid progressive angiopathy, as has happened in his series. We have had the good judgment, from the patient's standpoint, or perhaps poor judgment from the standpoint of statistics, to treat an eye which has seemed to be threatened suddenly with loss of vision. I would like to report that our experiences closely mirror Dr. Okun's.

Dr. Kohner: I would like to pose a question to Dr. Straatsma, who said that one of the reasons for coagulation is to eliminate ischemic areas responsible for proliferative lesions. Do we now know that it is ischemia which causes proliferation? I thought this was not certain. Certainly, we all see patients with areas of capillary closure, and new vessels developed in the area, but I thought most of us have seen new vessels in areas which were relatively well perfused. Also, I am not aware of any study where oxygenation of any particular area of the retina has been studied in detail. I want to know what our evidence is for ischemia being responsible for new vessels.

Dr. Straatsma: You are referring to a simple listing of the reasons given by the people who photocoagulate (ch. 51). They didn't present evidence. They simply indicated their rationale, and, indeed, I know of no evidence to really establish this. The only purpose for

bringing up rationale is that it probably gives us the first insight into indications and treatment techniques. But there is no evidence that that or any one of the other things I listed are indeed established facts in the pathogenesis of diabetic retinopathy.

Mr. Dobree: On the question of the role of ischemia in the production of proliferative lesions, it has always been of interest to me that lesions on the disc occur. This is the place that you wouldn't expect proliferation if it were an anoxic phenomenon. It is possible that there is some other completely different mechanism such as anastomotic vessels.

Another place you get these larger areas of new vascularizations is about one- to two-disc diameters away from the disc, along the main vessels. There is a very strong analogy, I think, between some of the cases we see of incipient venous thrombosis, where you get closely similar vessels to the ones we see in proliferative retinopathy. There is a possibility that what is going wrong here in proliferative disease is the slowing of the retinal circulation. This may well start on the arterial side or may be back pressure from the venous side. It may be more a pressure effect than an anoxic effect.

Dr. Spalter: If we accept the role of vitreous contraction, if we accept the fact that the new vessels on the surface of this interface between vitreous and retina start to bleed, then we should be trying to design a prospective biologic study to prevent these hemorrhages from occurring. We will then follow up those eyes after treatment with photocoagulation, whether by a laser or xenon photocoagulation. In our prospective study we can argue that one item of importance is to prevent vitreous hemorrhage. One straightforward way of accomplishing this is purposeful photocoagulation of nests of new vessels as they sit on the retina, in anticipation of Dr. Davis' well-described contraction of the vitreous (whereupon these vessels commence into the bleeding phase).

In a well-documented and planned prospective study, one would like to avoid any red cells in the vitreous, only by virtue of trying to establish whether or not preventing vitreous hemorrhage may ultimately improve the future course of these devastating retinopathies.

Dr. Leopold: Perhaps many of the clinicians who are not ophthalmologists would like some guidelines. If they recommend that their patients consider photocoagulation, what is the possibility of loss of visual acuity following such a procedure? What are the chances of the procedure itself causing damage? We have seen the complications Dr. Straatsma listed for us, but how frequent are these? How do you judge whether they may occur?

Dr. Okun: The primary visual complications are directly related to

the status of the eye at the time we initiate therapy. If we are treating an eye which we in the O'Hare Classification,[1] have called N_1 (which represents surface neovascularization of four or less areas and less than four-disc areas in amount) with no contraction of the vitreous, then the incidence of complications is extremely low.

I'm sure it would be possible, due to error on the part of the photocoagulator, to burn the macula. If these coagulations are done as I think they should be done (under retrobulbar anesthesia with the eye completely quiet), I can't see that this could happen. If one gets overly vigorous and approaches the macula much too closely and with much too intense a burn, then the macula can also be affected, but this is again just a matter of poor technique.

The other complications that I have seen are related to the therapy of more advanced disease. When membranes are present within the vitreous, when the vitreous has already contracted, when there is blood in the vitreous, there is no question that more heat is generated within the vitreous. The membranes can contract somewhat, and this can initiate even more hemorrhage. The realization of this status of the eye requires one to perform his coagulations with much less energy and thus with relatively little effect on the vitreous. I have seen retinal detachment occur within 4 weeks of photocoagulation in such eyes, but not recently. I think that these eyes were overly treated. I have seen retinal detachment occur more frequently in eyes which have not had photocoagulation, but which ran afoul for other reasons. Retinal detachment is the natural sequence of events following firm contraction of the fibrotic tissues which replace the neovascularization in these membranes. I have seen a case of presumed optic neuritis, an unexplained case of optic atrophy which had been photocoagulated, and she lost a fair amount of vision. For people who treat directly on the disc, a heat optic neuritis has been described with some lasting decrease in vision.

In general, I believe that the complications of photocoagulation are fairly minimal, if one is aware of the status of the vitreous at the time one undertakes therapy.

Dr. Larsen: I fully agree with Dr. Okun in his statement that in early proliferative retinopathy complications are few if you are not too vigorous in your treatment.

Dr. McMeel: Our series had, I think, cases that are a bit more advanced, and we have had two instances of preretinal fibrosis that has developed about 8 weeks after photocoagulation. In one instance, we have had a large vitreous hemorrhage which never really cleared up. This occurred the first night after photocoagulation.

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[1] O'Hare Classification, p. xxi.

It's worthwhile saying something about the field defects which certainly do occur. However, unless the defect is within about 20° of the fixation point, it's amazing how little subjective feeling of constriction the patient has. We do fields pre- and post-operatively, and it's quite amazing to see patients who really are unaware of marked field defects.

With regard to walling-off detachments, I personally feel this should not be done. As Dr. Okun intimated, he has also seen some cases where a retinal hole has been produced in association with the photocoagulation. I don't think this necessarily has to be due to the photocoagulation burn at the time. But if photocoagulation is near the edge of a tented-up area of retina and produces a wider area of elevation, traction continues, and we have seen a hole formed right at the edge of photocoagulation where the retina had been scarred down. In other words, a relatively limited secondary detachment has been converted to a total detachment.

Dr. Aiello: The ruby laser does not require retrobulbar anesthesia. In our series of some 130,000 laser applications, no macular lesions were made. With regard to complications, the only ones seen were early in the use of the instrument. Small, minute hemorrhages occurred at the site of the laser photocoagulation if the setting was too high or if you treated over a lesion that had just been made. We didn't feel that complications contributed to the progression of the disease in more than one or two cases.

As Dr. McMeel mentioned, we have not felt the laser to be helpful in the treatment of detachments.

Dr. Beetham: Of the laser treated eyes, we have 14 percent who became worse with treatment. About 86 percent either remained stable or improved. We took as our controls the opposite eye of each patient (when there was an opposite eye), and we have treated both eyes of only four people. One was the daughter of a Philadelphia lawyer who practically forced us to do so because the treated eye showed such great imporvement. In the untreated group 43 percent became worse, and there were four that we graded as improving but not treated.

Dr. Leopold: That doesn't really answer the question yet.

Dr. Okun: When we were trying to figure out some rationale for our finding that photocoagulation seemed to benefit eyes, we learned about two diabetics who had extensive diathermy procedures for retinal detachment some time before, who, 10, 15, or 20 years later, developed a florid retinopathy in the opposite, untreated eye.

Dr. Fraser: I wonder whether we could hear some comments on the fairly large group of eyes that haven't changed. We hear that some improved and a smaller number worsened. Concerning the bigger

proportion, who presumably retained their proliferative retinopathy, can the observers tell us whether they think this was not reversible because of its appearances, or was it because these were eyes which had so much involvement that you couldn't destroy all the disease process. Is it not possible to say whether they needed more laser treatment or more photocoagulation? Can we know whether there is any way of telling from the outcome of these experiments whether more treatment might have helped or whether we can tell which are reversible lesions?

Dr. Aiello: Most of our cases fall into the earlier proliferative retinopathy (in the early vascular stage). The ones that didn't improve, that remained in the same classification or become worse, were those that were in the N_2 classification[1]. The vast majority of the N_2 classification, however, went on to either N_1 or to no diabetic retinopathy. These N_2 cases are still an early stage compared to those with elevated retinal vessels that are treated with the other type of photocoagulation.

For laser coagulation to be indicated, lesions had to be flat on the retina, not elevated, and without traction. The few that had fibrosis or the few that had extensively elevated new vessels from the disc resulted in miserable results.

Dr. Leopold: Has anyone on the panel any data on studying these eyes other than by visual acuity and perimetry? Have you got tonographic data or any other data on these patients suggesting that photocoagulation has done something to these eyes other than close off a few blood vessels?

Dr. McMeel: Over the last few months, Dr. E. Wolf at the Massachusetts Eye & Ear Infirmary has done a semiobjective measurement of the Tyndall effect in the eye, both before the photocoagulation and then following the photocoagulation. There are a few eyes that seem to show a decrease in the in the Tyndall effect. We feel that this is a true decrease in the Tyndall effect, because Dr. Van Heuven did very complete vitreous studies beforehand, and only the ones that had only no red cells in the vitreous were studied by Dr. Wolf.

Mr. Dobree: I think that there are some preventible secondary effects that we haven't dealt with. There are connective tissues which form around the new vessels if they are not coagulated. For example, the scimitar shaped band(s) (see figure p. 621) is composed partly of retinal and partly of vitreal elements. It is formed by traction between two fixed points; in this case between a focus of cicatricial tissue near the disc at (a) and cicatricial tissue forming around vascular arcades at (b). It would have been prevented had the vascular arcades below been photocoagulated before cicatricial tissue had developed around

[1] O'Hare Classification, p. xxi.

them. These bands are completely avascular from the start. The surrounding retina obviously is in great danger of being pulled right off. This is the kind of situation which is very likely to cause a series of hemorrhages.

Dr. Leopold: It's obvious that there are a number of individuals who are rather convinced that photocoagulation or laser therapy has a potentially beneficial effect on retinopathy, and that they all agree, I believe, that there is still a need for controls, and that we need much more time before we can really tell whether this is going to prove to be an effective form of therapy. Certainly the work of Dr. Caird, Dr. Beetham, and Dr. Davis on the natural history of diabetic retinopathy would bear that out.

Dr. Straatsma, in going over these papers there are certain things which must have become apparent to you which should be done or are definitely needed in further pursuit of this approach to diabetic retinopathy.

Dr. Straatsma: That is, of course, a difficult, spirit of the moment question, Dr. Leopold.

Dr. Leopold: I never challenge anybody if I don't think he can give the answer.

Dr. Straatsma: What we need to do is plan to reconvene, because, as was brought out very properly by both Dr. Beetham and Dr. Caird, we must wait for a longer period of time before we can really be cer-

tain of the efficacy of this treatment. I would like to stress, though, that I believe the criteria presented in my summary (ch. 51) should be adhered to before making a judgment regarding the efficacy of the treatment. First, there should be a comparison between treated eyes. Second, there should be a comparison between treated eyes and the natural history, because either of those criteria by itself could be misleading. I don't think that we could postulate a situation in which, if both of these criteria are met, that we have made the wrong conclusion. In dealing with the experiences with photocoagulation, which vary from the average of 2½ years or so to the data Dr. Beetham has presented on 5-year prognosis, we are indeed extrapolating to some extent. We must be very careful, because this could be misleading. Yet, this represents the state of the art today.

Dr. Okun: I would like to say one word on comparison with previous series. It's become quite apparent to all those who work a great deal with diabetics that, in order to compare series, one must know the stage of the retinopathy at the onset of treatment. This is simply another reiteration of the fact that these eyes must be classified very, very carefully. No one will question the fact that the 5-year visual acuity is extremely important, but whether our 5-year results will match those of Dr. Beetham's, I don't know. I can certainly pick out a group of patients (characterized by, perhaps, some changes on fluorescein or, perhaps, some very early, minimal, proliferative changes which we have all seen to undergo spontaneous regression), who I will subject to absolutely no therapy, and I am certain that this group will do better than the group that we have chosen to treat thus far. Thus, I would like to state that the important information that will come with long-term followup is not from a comparison to a previous series, but information that will come from the uniocularly treated symmetrical cases.

Dr. Beetham: Just a minute. We started out to do just one eye of each patient, but are we in a sort of legal position for not treating the patient properly if the treated eye becomes good, and the other eye is getting worse? There goes our control.

CHAPTER 52

Summary of Papers on Treatment Techniques in Photocoagulation

EDWARD OKUN, M.D.

The experience gained in the photocoagulation therapy of well over 1,500 eyes is represented in the 13 groups who have analyzed their results for this conference. Eleven of the papers concern the effects of xenon arc photocoagulation with the West German Zeiss photocoagulator, while two groups report on the use of the laser for creating chorioretinal lesions. The criteria for selection of patients for therapy differed somewhat. Also, the areas treated differed. Several groups appeared to wait for progression of retinopathy before undertaking therapy. The paper of Wessing and Meyer-Schwickerath (ch. 48) indicates that two-thirds of their patients had essentially background retinopathy, and therapy was aimed primarily at the improvement of macular function or at decreasing the incidence of vitreous hemorrhage.

Retrobulbar anesthesia was preferred by those who used the xenon coagulator. Laser treatment did not require any anesthesia. The pupils were well dilated, and most operators working with the Zeiss photocoagulator used either the 4.5° or 6° field opening with a basic setting of 1 or 2. The field settings decreased for more central work, and increased in cases of poor media and more peripheral therapy.

There was essential agreement that the photocoagulation lesions be directed to the areas of visible neovascularization. The end point of coagulation was a retinal effect varying from yellowish to greyish to white. Mr. Dobree preferred to see only a choroidal effect (ch. 37).

Cleasby (ch. 36), Mortimer (ch. 41), Roth (ch. 43), and Wetzig (ch. 49) preceded each photocoagulation session with an intravenous fluorescein injection, claiming that areas of leakage could be better detected in this way. Of this group, only Wetzig has been successful in materially altering the blood supply of intravitreal proliferating membranes by treating them during the stage of fluorescein staining.

Several studies reported vitreous contraction following treatment of membranes with either subsequent increase of hemorrhagic activity, further retraction of membranes, or even retinal detachment occuring shortly after photocoagulation therapy in cases of extensive membrane formation.

Neovascularization of the disc and adjacent to the disc has been attempted by Drs. Mortimer, Wetzig, Dobree, and Okun (ch. 42).

More energy than usual is required in this location, occasionally resulting in severe, although temporary, visual defects. Occasionally, the visual defects are permanent. Mortimer has referred to this as a heat optic neuritis. The results of therapy of neovascularization in this location are not as satisfactory as therapy at other sites. Figures 1a–b illustrates the effect of photocoagulation on neovascularization in and above the disc. In this location the nerve fiber layer is extremely thick, making it very difficult for the lesion to come all the way through. Extensive coagulation in this area can lead to symptomatic sector field defects. Eight months after photocoagulation a shunting channel has replaced most of the bare neovascularization previously seen in this area.

Treatment can be directed fairly close to the macula without obtaining a decrease in macular function (fig. 2a–c). The neovascularization shown in figure 2a would become very difficult to obliterate if one waited very much longer. Figures 2b–c shows the effects of photocoagulation at 1 day and 8 months after treatment. This patient maintains visual acuity of 20/20 with lesions fairly close to the macula. Several groups stated that they were able to place very small lesions within one-half disc diameter of the macula without loss of central acuity. In these cases, a small scotoma could be plotted corresponding to the chorioretinal scar.

In patients who have experienced either preretinal or vitreous hemorrhages, Cleasby, Harris (ch. 38), Mortimer, Okun, and Johnston apply photocoagulation to the bleeding site if it can be located. Figures 3a–b shows the effect of photocoagulation directed to the bleeding site. Several days after photocoagulation the blood had cleared and the situation appeared to be under control. If the bleeding site could not be located, and the preretinal hemorrhage was rather small, it was assumed that the bleeding occurred from vessels obscured by the blood, and in this case the blood itself was coagulated. Vitreous traction can frequently be observed to be the causative factor in these hemorrhages. McMeel and Van Heuven (ch. 40) felt that vitreous traction was somewhat a contraindication to photocoagulation, and, therefore, did not strongly advocate photocoagulation treatment of traction hemorrhages.

Okun, Johnston, Wetzig, and Jepson, attempt to obliterate all visible areas of neovascularization and hemorrhagic activity, treating all four quadrants at one sitting. The maximum number of lesions applied at one sitting varied from 20 (ch. 39), to 300 (Wessing and Meyer-Schwikerath, Okun, Johnston, and Aiello, (ch. 35). Several of the groups prefer to perform photocoagulation at more than one sitting rather than place many lessions at one time.

FIGURE 1a.—*Neovascularization on and above the disc.*

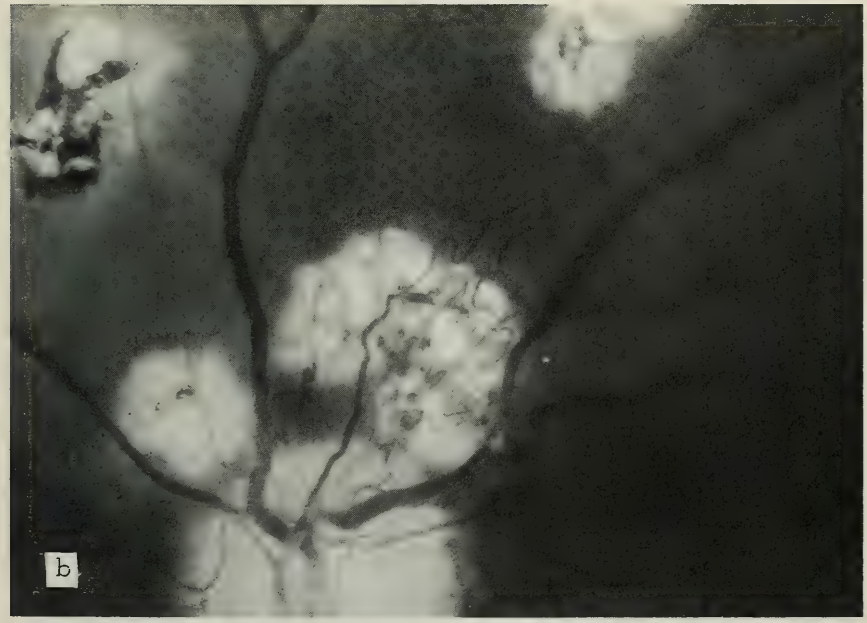

FIGURE 1b.—*Upper one half of disc and adjacent retina 2 years after photocoagulation.*

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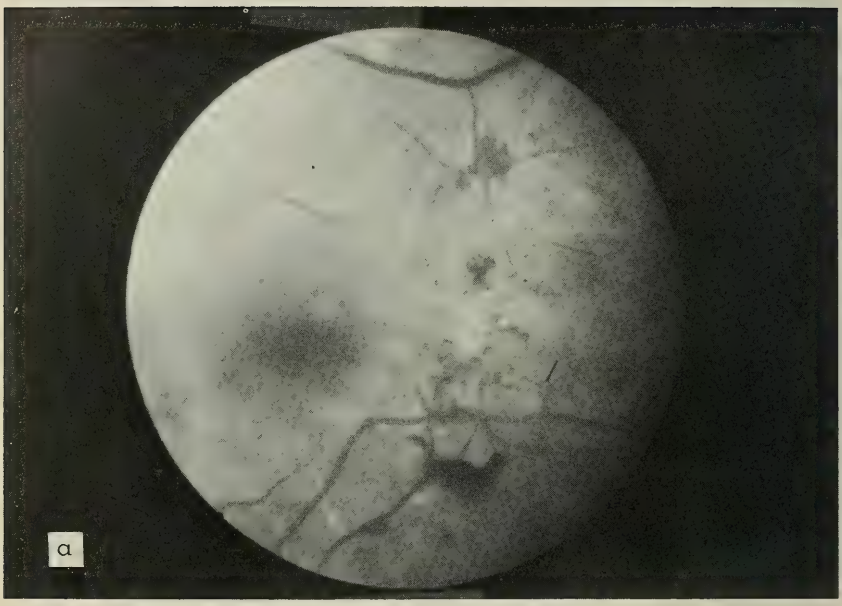

FIGURE 2a.—*Neovascularization temporal to the macula.*

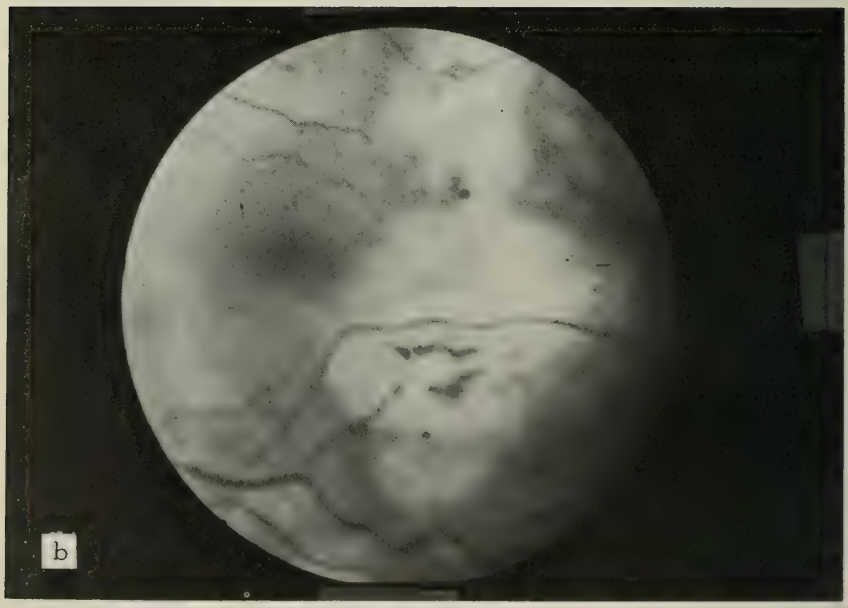

FIGURE 2b.—*Same area 1 day after photocoagulation.*

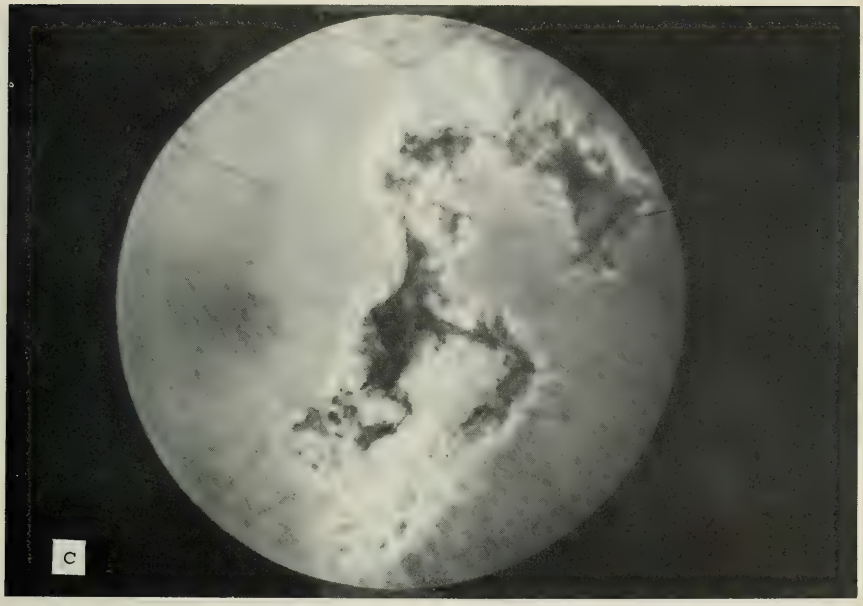

FIGURE 2c.—*Same area 8 months after photocoagulation. Neovascularization has been eliminated and replaced by chorioretinal scar.*

Localized retinal detachments were walled off by photocoagulation lesions, as were areas of marked vitreous traction with impending retinoschisis and/or retinal detachment.

Aiello *et al.*, claiming that the laser causes less vitreous contraction, used this modality for placing disseminated lesions over the posterior pole. Therapy was concentrated over areas of active neovascularization. However, the intended purpose of this spray type of treatment was to produce an eye which resembled one affected by disseminated chorioretinitis, a condition which appears to protect an eye against severe proliferative changes. However, they did not feel that this type of therapy was effective in cases of traction type hemorrhages or when the neovascularization was pulled forward. Xenon are photocoagulation appeared to be more effective for this latter type of case.

Zweng (ch. 50) used the laser much the same way as the xenon arc photocoagulator in the therapy of proliferative retinopathy. He concentrated on dehydrating the macular area by the elimination of abnormal zones of leakage. Wessing and Meyer-Schwickerath, Welch (ch. 47), Wetzig, Cleasby, and Okun used the xenon arc photocoagulator for the same purpose.

Patients were followed generally at 6 weeks to 3 months intervals, and repeat photocoagulation was performed when necessary.

FIGURE 3a.—*Site of origin of vitreous hemorrhage.*

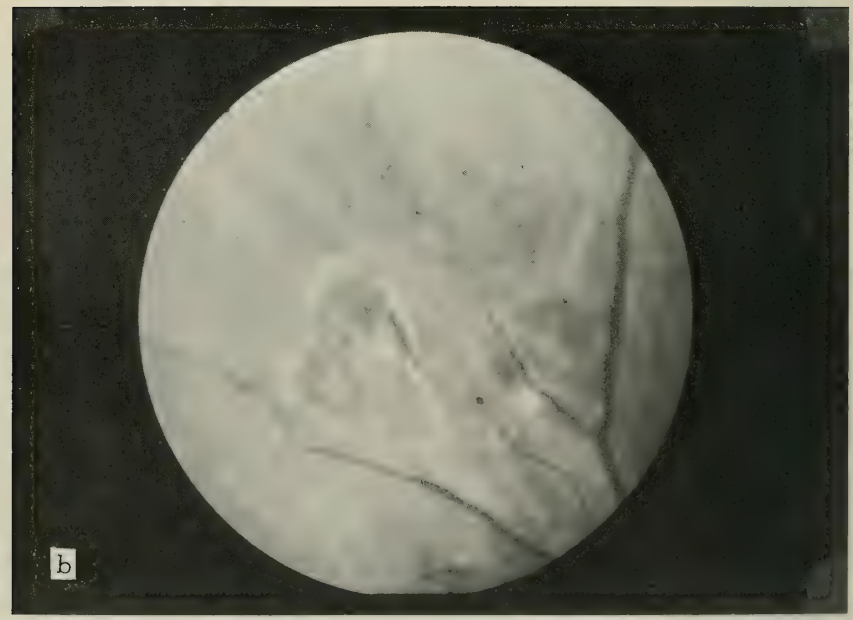

FIGURE 3b.—*Site of photocoagulation scarring 1 month after treatment.*

The complications of photocoagulation were listed in a number of the papers. (See table 1.)

TABLE 1.—*Complications of photocoagulation treatment for proliferative diabetic retinopathy (PDR)*

1. Iritis (mild).
2. Viterous hemorrhage (vitreous retraction).
3. Retinal detachment.
4. Accidental macular burn.
5. Maculopathy—vitreous fibroplasia.
6. Complication related to retrobulbar injection;
   (*a*) Retrobulbar hemorrhage:
   Vein occlusion.
   Optic neuritis.
7. Retinal vein and arterial occlusion.

Discussion of Treatment Techniques of Photocoagulation

PAUL C. WETZIG, M.D., *Moderator*

Dr. Wetzig: We should have the opinion of the panel on exactly when to start treatment.

Dr. McMeel: We have been treating, I think, more far-advanced lesions than many others. In the last few months my feeling has been that we should treat earlier and earlier and, seeing some of the work that has been presented here, possibly even earlier. However, to date, I have been mainly confining my treatment to areas of neovascularization once they appear.

The following are the ideal conditions for photocoagulation. Anything that starts deviating from these, I think, makes the prognosis worse and the indications for treatment less. First of all, you should have media which are as clear as possible. Therefore, if you have had a recent bleeding episode, I personally feel it is worthwhile to wait a few days, particulary if this is an initial episode. The lesion should be flat, because it is at the level of the pigment epithelium that you have your maximum heat absorption, although with the xenon arc you get a great deal of heat absorption in the blood vessels themselves. If the lesions are elevated, however, the chances of getting an adequate heat absorption, I think, drop off rather rapidly. It has been my experience that the treatement of vascular lesions elevated into the vitreous cavity is rather poor.

I have mainly been treating vascular lesions. If there is a great deal of fibrosis, your chances of success are relatively less. We have been treating away from the macula and posterior pole, and we have been treating discrete lesions rather than massive areas. There are very few cases which fit the ideal.

Dr. Wetzig: Dr. Wessing, your group elected to treat only the early stages of the disease. What has been your reason for this? Do you feel that the more far advanced cases will not benefit?

Dr. Wessing: We had the impression that photocoagulation on advanced cases didn't work.

Dr. Wetzig: We also have some divergence of opinion regarding the exudative type of disease. By this, I mean the disease characterized by so-called hard exudates. Dr. McMeel has stated this group is not suitable for treatment. We have found there are some members of the panel who have a different opinion.

Dr. Spalter: Many of our internist colleagues will agree that spontaneous resolution of hard exudates always leaves damage to the receptor elements of the retina. Whether or not we can effectively resolve the exudates more rapidly than one would expect from the natural course of the disease becomes, I think, a very moot and unimportant point because it is my impression that they are very much akin to the exudates we see in senile macular degeneration. Too often, when they do clear and when we are able to observe the character of the retinal pigment epithelium, there is atrophy.

I think that when to start treatment is the most provocative question? The ophthalmologist can start only when the patient is presented to him either on his own (because of visual problems), or as a diabetic, recognized by internists and general practitioners who appreciate the problem. We are not starting with the ideal Utopian situation of prophylactic medicine, but are presented with the fact that retinopathy has already compromised vision to a degree. Therefore, too often the patients will arrive with worse than N_1 F_1 (according to the O'Hare Classification [1]).

There seem to be two groups here: those of us interested in treating specific lesions in the retina (neovascularization, early proliferans, *et cetera*) and those who want to reduce the metabolic demand of the retina by massive destructive approaches to all peripheral retinal areas, sparing the vital central area of the macula. Regardless of which approach one would take, we don't have the ideal situation of treating the early simple retinopathy. The question of when to treat, will be answered when an education program in this country comes along whereby more people look at the fundi of diabetics carefully and refer them to whichever mode of therapy they think effective, whether it be the neurosurgeon or the ophthalmologist. Not enough in the United States today are looking at retinas early enough in this disease entity.

Dr. Wetzig: I would like to ask Dr. Okun when he decides not to treat the advanced cases in the N_2 F_2 classification.

Dr. Okun: You know I never refuse a case. Photocoagulation has its indications and contraindications. I really feel that I have not done too much for patients who are N_2 F_2 and who have a fair amount of hemorrhage in their eye to begin with—not by photocoagulation. There are, however, other approaches to this type of disease. We are thinking

[1] O'Hare Classification, p. xxi.

and feeling that there is something wrong with the relationship between the vitreous and retina in these cases where the vitreous is so contracted, and we have moved over to the field of scleral buckling procedures for some of these patients (see below). It is still quite experimental, but we really have nothing more to offer.

However, in a case with extremely advanced retinopathy where there is a hemorrhage whose source is easily seen, then those cases, I think, can be helped by photocoagulation. There are other times I wouldn't treat by photocoagulation, because certain cataracts make it impossible to photocoagulate. When you can't look in with an ophthalmoscope, you can't reat with a light coagulator.

Dr. McMeel: I would like to ask Dr. Okun a question. If you see a specific bleeding point, but this bleeding point is on the tip of an area of vascular angiopathy sticking well out into the vitreous cavity, do you go for it? If so, how do you approach it?

Dr. Okun: With a contact lens. I try to find out what refractive change will bring the beam into focus at that area. I have been able, on a few occasions, to stop the bleeding. However, the prognosis is still terrible, and I am not sure how much good we are doing.

Dr. Davis: What do we do with these patients after their retinas detach?

Dr. Okun: We would, of course, love to be able to limit our therapy to the early stages of diabetic retinopathy. Unfortunately, some patients do not come to see us until they have quite advanced disease, and others become advanced despite early therapy. Retinal detachment is one of the complications which leads to blindness if not corrected.

It has been the general feeling in the past that unless there was a break in the retina, these detachments were best left alone. Our experience over the past 8 years indicates that purely traction type retinal detachments should be operated upon as soon as possible after loss of macular function (Okun, E. and Fung, Wayne E.: "Therapy of Diabetic Retinal Detachment," presented at the 17th annual session of the New Orleans Ophthalmology Society Symposium on Retina and Retinal Surgery, Feb. 11–16, 1968). A volume reducing operation with infolding of the sclera toward the area of most marked proliferation has resulted in excellent functional return in some patients and return of "walking" vision to many. Table I shows the type of procedure used and the evaluation of our results in the therapy of our first 50 cases.

Table II indicates that purely traction type detachments have done as well as those with retinal breaks.

Once fibrotic changes have occurred within the vitreous cavity, there remain only two mechanical means for the release of traction: (1) cutting the membrane, and (2) reducing the distances between trac-

TABLE I.—*Surgical procedures used in the treatment of diabetic retinal detachments*

Type of buckling	Number of eyes	Number of eyes with useful vision	Percent	Average length of followup in months	Number of eyes with 20/400 or better	Percent
Encircling with resection	34	22	65	32	16	
Encircling without resection, but with plombage	7	5	71	18	1	
Episcleral encircling	4	2	50	13	1	
Resection alone	5	4	80	46	2	
Totals	50	33	66	30	20	40

tion points. Intravitreal membrane lysis in diabetics is very risky because of the vascularized status of most of these membranes. However, scleral buckling procedures are well tolerated by the diabetic eye. A buckling procedure relaxes taut diabetic membranes in two ways. First, it reduces the distance between the vitreous base and the point of greatest retinal elevation; i.e., the area of greatest traction (fig. 1). Secondly, the intravitreal volume is reduced, allowing the formed vitreous to take up a great portion of the vitreous cavity, thus forcing the effective anterior traction points further posterior. This can be thought of as a relative vitreous expansion, just the reverse of what occurs with vitreous contraction.

Vitreous hemorrhages from blood vessels which have been pulled up into the vitreous are very difficult to treat by photocoagulation, since it is almost impossible to occlude these vessels, either at the vitreous traction point or at their base. Relief of traction at the tips of these vessels by means of a scleral buckling procedure seems logical.

Our short-term followup is good, but it is still very short. The most satisfied patient is one who had experienced four severe vitreous hemorrhages which brought her visual acuity down to hand motions over the previous 6 months. When her vitreous had cleared, we performed an episcleral encircling procedure on this eye without drainage of subretinal fluid. Two weeks later there was a marked relaxation of the vitreous membrane that had pulled several of her blood vessels in toward the center of her vitreous. During the past 6 months she has had only one minor hemorrhage and maintains visual acuity between 20/25 and 20/40 in this eye. However, careful reexamination at the

TABLE II.—*Postoperative results as related to the presence or absence of retinal holes preoperatively*

Preoperative condition	Number of eyes	Number of eyes with useful vision	Percent
Detachments without breaks	29	19	66
Detachments with breaks	19	12	63

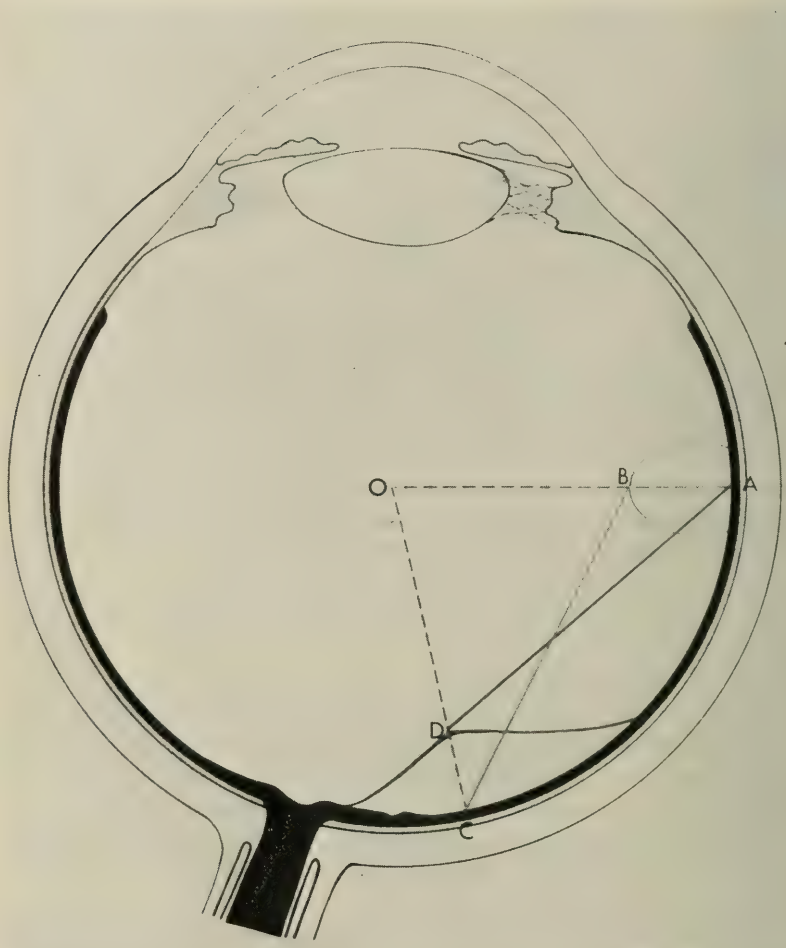

FIGURE 1.—*Schematic sagittal section of an eyeball showing that an inward displacement of point A to point B allows point D to fall back to point C. This assumes that vitreous traction forces run in the direction of AD before scleral buckling, and BC after scleral buckling.*

end of 6 months has revealed that the process of membrane shrinkage seems to be continuing, and the membranes are not as lax as they were shortly after the operation was performed.

We have now done encircling buckling procedures without drainage on 17 eyes with localized vitreous traction detachments. In each instance, the detachment has either decreased in size or completely subsided despite the fact that no subretinal fluid was drained. One patient had a central vein occlusion postoperatively, possibly due to extreme elevation of intraocular tension.

The question as to whether or not these people should have cryotherapy or diathermy along with the encircling element is not entirely resolved. We had noted a marked decrease in the incidence of hemorrhagic activity following the buckling procedures done for retinal detachment. Whether this could be attributed entirely to the change of the shape of the globe, or whether, indeed, we had accomplished the same type of controlled retinal ablation as is done with coagulation is uncertain. However, I can tell you that in our last three cases we combined either photocoagulation or cryotherapy with the buckling procedure.

Dr. McMeel: I would like to comment briefly on Dr. Okun's surgical treatment. I think this has a very definite place in a limited number of cases, but to keep it in proper perspective, I would like to make these comments. I have 180 patients who had proliferative retinopathy. Of these 180, there were 14 who had a decrease in the amount of secondary detachment. Almost 10 percent had a decrease. One thing we have to remember is that this is a fluctuating disease, as Dr. Okun also intimated. Also, we have to differentiate between the rhegmatogenous detachment and the secondary detachment. In the examination as a whole, the slit lamp and contact lens are extremely important because there are so often very small holes in the posterior part of the retina (within 30° of the disc) which can be seen only with the slit lamp and contact lens. You have to search for these most carefully. In a situation like that, an equatorial buckle will result in failure, but, in well selected cases, probably has a place.

Dr. Okun: I just want to say that we did go over our retinal detachment cases quite carefully, and we still feel that the nonrhegmatogenous cases do as well as the rhegmatogenous, probably because those breaks are so far back that they are very difficult to close.

Dr. Van Heuven: We have just started to do the kind of procedure that Dr. Okun has described. All we currently have is a theoretical suggestion that if we examined the vitreous, we could find specific points of traction and then be tempted to buckle those areas. I just wonder if that might even produce better results.

Dr. Spalter: At the ultrasound laboratory at Columbia University, Dr. Coleman, who is in charge of this work in collaboration with myself, has been considering its potential uses. It is well known that ultrasound will lyse red blood cells quite readily. It is also believed that ultrasound may satisfactorily liquefy the vitreous. If we could expedite the clearing of the vitreous, we might add an additional therapeutic parameter to all of our efforts.

We can bend the ultrasound energy with prisms in order to avoid its going through the cornea. We should prevent its going through

the pupillary space to avoid cataracts. Experimental work in rabbits can possibly be applied to humans, but it has not, as yet. Baum, in 1957, tried it with very simple experiments, not related to diabetic retinopathy, but just explored the potential uses of ultrasound.

Blood in the vitreous can be tagged with radioactive chromium, and the decay rate of the blood in the eye can be quantitated. The absorption or disappearance of the radioactive particles from the eye is expedited by a factor of about 50 percent after using ultrasound.

Dr. Davis has suggested that vitreous contraction plays a significant role in proliferative diabetic retinopathy. I think we are all agreed on that. If we were sitting here speculating for a prospective study, could we not, in anticipation of vitreous contraction, liquefy the vitreous body sufficiently so that there were no longer any interfaces between the vitreous and these new vessels? When one places radioactive dye in an eye, and immediately thereafter applies ultrasound to the vitreous, the dispersion of dye is quite evident within 5 minutes or as soon as an X-ray can be made.

Dr. Norton: How about the work that Coleman did about 15 years ago, in which he liquefied the vitreous by applying ultrasound, but in which the retina was also disturbed?

Dr. Spalter: Dr. Donn did that work. He is still Dr. Coleman's severest critic. The energy levels used were such that there was no focusing ability on the ultrasound. Therefore, anything put into the vitreous bounced right through and hit the retina. The hope is that the electronic gear available today can actually focus this ultrasound energy wave to a pinpoint and can direct it where you wil. The objection to the dangers of ultrasound are well taken.

Dr. Davis: Dr. Sweet wanted me to pose this question: "Is the retraction of the vitreous due to partial liquefication and collapse of the framework? Why should further disruption of the vitreous gel help, unless the framework is broken?" I am sure what everyone who poses this argument is saying is that the new vessels become adherent to the framework of the vitreous. They don't seem to become adherent to the liquid vitreous. In other words, if man were made with a completely fluid vitreous instead of a gel, maybe there would be nothing for the vessels to get stuck to. I am not advocating that we use ultrasound to liquefy everyone's vitreous, but I think Dr. Spalter should be encouraged to pursue this further.

Dr. Wetzig: We will go on to a discussion of instrumentation, as it has a bearing on the effect of the treatment. The laser people seem to have the best press agent. Most patients think they are being treated by laser. They have never heard of the xenon arc. So we will ask Dr. Zweng to tell us his experience with the laser.

Dr. Zweng: One might well ask the question, Why should anyone go to the trouble of developing a laser photocoagulator in the first place, when xenon arc photocoagulators were in the field and performing as well as they have been? I think we all owe Meyer-Schwickerath and his group a tremendous debt of gratitude for developing light coagulation. The answer to this question was included in the material presented by Dr. Straatsma and by Dr. Okun concerning the complications of photocoagulation. I believe none of the complications therein listed came from laser photocoagulation. I believe they all came from xenon arc photocoagulation. So, if xenon arc photocoagulation worked reasonably well in many instances, still there were and are problems connected with its use, and the idea is always to improve.

What were the things about laser light that made it, at least theoretically, better as a source of light for photocoagulation? First of all, we have to remember that laser light is like other light in most ways. It is reflected, refracted, absorbed and dispersed like incoherent or ordinary light. But it does have a couple of special characteristics that are useful in photocoagulation. First of all, it is a very intense light. That means that a burn can be obtained with a very, very tiny amount of energy because it is squeezed into a very, very tiny amount of time. Typically, with the present three ruby laser photocoagulators (American Optical, Optics Technology, and Keeler), the pulse lengths are 200 to 400 milliseconds in length. This means that a useful effect can be obtained, as I said, with a very small amount of energy. When I say "small," I am talking about 10, 15, 20, or 25 millijoules of energy. Indeed, in treating macular lesions we customarily have each pulse of our instrument logged and recorded, so we do know the output of each and every pulse, and about four millijoules are used in the treatment of macular diseases.

By contrast, the xenon arc photocoagulator that we have had at Stanford since 1959, put out exactly 2 joules or 2,000 millijoules using the basic setting of I, 4.5° field, with the zero iris aperture for 1 second. For similar work with laser photocoagulation, 25 to 59 millijoules are used. That is a large energy difference. I think it accounts for complications that one occasionally—I hasten to add, not frequently—runs into with xenon arc photocoagulation.

Now, the other laser characteristic which I wish to allude to is wavelength specificity. The histopathology of laser coagulation indicates the gentleness of the lesions. This is work we reported several years ago on a patient who had to have his eye enucleated because it harbored a malignant melanoma of the choroid. We submitted him to laser photocoagulation to get the histological appearance of these

lesions. The visual epithelium did stick to the pigment epithelium everywhere the laser lesions were present. The visual retina was pulled off from the pigment epithelium by the cutting knife everywhere else. But we were most struck by the gentleness of the lesion at the level of the pigment epithelium with radiation of the heat forward into the outer layers of the retina, but sparing the interior layers of the retina. The way we have been using laser photocoagulation differs from the way Dr. Aiello and Dr. Beetham have been using their laser photocoagulator. We treat aneurysms, small hemorrhagic areas, and small neovascular tufts.

Dr. Wetzig: Are you treating the vessels which apparanently lead into these aneurysms?

Dr. Zweng: No; the aneurysms themselves. Directly on the aneurysms. This, I think, differs from the way Aiello has been treating. We do treat in the macula.

Dr. Wetzig: I specifically would like to know whether Dr. Aiello is directing his laser to vessels. If so, what size are the individual vessels? What noticeable effect occurs in the first 2 weeks following treatment?

Dr. Aiello: Several years ago, in 1963 or thereabouts, Dr. Beetham mentioned that he had noted, with others, the fact that chorioretinitis patients and other patients with myopia and advanced glaucoma did not seem to develop the proliferative phase of retinopathy if they developed diabetes. Further, it was noted that hitting individual lesions when they first appeared, as Dr. Wessing has mentioned, merely resulted in new lesions occurring in other areas of the retina at a later time. With this in mind, Dr. Beetham formulated the concept of whether there was an instrument we could use to produce chorioretinitis throughout the posterior pole without causing significant field loss and without significant complications. When Dr. Zweng, Dr. Campbell, and others promoted the ruby laser, which produces a deep lesion, we though that we should at least test this hypothesis, and see whether we can alter in any way the course of the retinopathy by reducing total retinal or changing the metabolism, whatever it may be.

The treatments are started by placing 200 to 300 applications in each eye at the first sitting. Patients undergo two, three, or four sittings, until a total of 600 to 1,000 applications are applied. The total number depends much on the extent of the retinopathy and the response to the retinopathy over this period. Each treatment is placed at 3- to 6-week intervals.

The macula, disc area, and the disc, itself, were not treated.

One of the curious things is the fact that much of the pathology may lie outside the disc-macula area, and we have had many patients like

this. We would, after treating those pathologic areas, go back and continue treatment, with the idea of preventing further progression of the disease.

Dr. Wetzig: I would like to know how you are managing these new fans and new vessels.

Dr. Aiello: Most of the patients we like to treat fall into our classification of group 2. These have areas of neovascularization flat on the retina, not elevated fans, and in these areas we treat right through these lesions. We will put confluent lesions in the area of these new vessels, so that we are treating the pathological tissues as well as the other areas of the retina.

Dr. Spalter: My knowledge of optics of the laser has suggested that a ruby laser is a red laser. Red lasers have red light, and pass freely through blood vessels. In theory, unless one lays down many layers of pigment proliferation so that you are getting closer to the surface of vessels and create heat in that area, ruby laser light should go through these nests of vessels on the surface of the retina and do no damage to them. This has a corollary advantage that one can march across the retina, as you have, and not affect too many of the vital arterioles.

Dr. Aiello: We don't deny at all that we are going directly through the red blood vessels. What we are trying to see by this treatment is whether we can alter the metabolic requirements, the vascular flow or what-have-you, by affecting the deep arterioles, where much of the pathology lies, and see whether or not this has any effect whatsoever on the overall retinal picture.

Dr. Wetzig: The question has been raised as to how much damage is done to these large vessels with the xenon coagulator. Several of the authors have commented they straddle the major veins in an attempt to avoid direct treatment on these vessels. I would like to know if bad results have occurred from striking these vessels. What is the advantage of treating them?

Mr. Dobree: May I make a comment about the paper of Dr. Aiello and the question of decreasing the metabolic requirements of the retina by multiple coagulations? We had a very similar sort of idea. We thought the simplest way of doing it would be by obliterating sectors or the whole peripheral retina at the equatorial area. We hit the arterioles very hard indeed, so as to get a quadrant area of ischemia. We eventually abandoned this, because, in fact, we got an arterial occlusion doing this.

Dr. Aiello: We can't get an arterial occlusion with our laser method, but there is some evidence that the smaller capillaries are being affected by this technique. Whether or not they would add up to a significant alteration in vascular flow is something we don't know at the moment.

Dr. Okun: There is no question that you can occlude a fairly good sized vein by a direct hit. This leads to a great intensification of the hemorrhagic phenomena distal to the vein. Sometimes, hemorrhagic activity can pour out into the vitreous as it sometimes does in vein occlusion. Branch vein occlusion, which will lead to neovascularization of and by itself, isn't what we want to accomplish. Most of the neovascularization, however, does come right off the vein, and you can straddle either side of the vein and knock all that neovascularization out, ending up with a vein that is much less engorged and less torturous, and, I think, have a good result.

I have actually found it somewhat difficult to occlude an arteriole. Thus, if there is neovascularization which crosses over an arteriole, I ignore it, and treat right over it. It knocks out that neovascularization very nicely. Occasionally there will be a late occlusion of that arteriole, but I haven't seen as much difficulty arise from that as I have from venous occlusion.

Dr. Roth: I personally attempt to avoid the large vessels, and go mainly for the small new-vessel formation.

Dr. Wetzig: Some of Dr. Okun's pictures demonstrated a striking difference in the caliber of the veins before and after treatment. Is this the usual finding that you notice, and how soon does this occur?

Dr. Okun: I wouldn't say this is the usual finding, but it is a finding. I don't know exactly what percentage of cases will show this, but I wouldn't be surprised if. when we go back and try to analyze the percentage of cases showing this, that the longer after treatment that we look at this, the more impressed we become in comparing preop and postop photos. In cases with tremendous amounts of neovascularization, where a large amount of therapy is placed in the retina, there is no question that you see this earlier. Even in cases where not quite as much therapy is used, if it is directed at areas of neovascularization, which probably do represent areas of localized shunting of blood supply, we do see this. It isn't surprising. When we treat angiomas in the periphery, which really are shunt vessels, the feeding vessel and draining vessel both decrease in size as the shunt is eliminated.

Dr. Welch: Concerning veins, I agree with Dr. Okun that you can go right alongside, and actually squeeze them down a little. You won't get a branch vein occlusion.

You don't have to worry as much about arteries, because, in cases of sickle cell C retinopathy, where we are trying to occlude an artery leading into a fan, it takes several treatments.

Dr. Oakley: I would like to ask Dr. Aiello about his ruby laser technique in producing the large number of lesions. The pictures he

showed us looked as if a comparatively normal area of retina close to the disc had been bombarded. I would like to know what type of lesions he is treating in this way and what effect this has on fluorescein appearances and what effect this has on the caliber and behavior of the larger, intermediate-sized vessels. Is there any evidence that producing these large numbers of lesions causes change in caliber or change in flow rate or change in vascular dynamics at the posterior pole of the retina?

Dr. Aiello: We may initially treat adjacent to the disc or in the peripheral retina, but eventually we will treat both areas. As there is a reduction in the number of the small neovascular patches and in the amount of angiopathy in general, there is also a decrease in the size of the veins. We have not measured these, but Dr. Beetham feels, and I would agree with him, that we are getting a decrease in the size of the vein if the angiopathy improves. If it doesn't improve, we are not seeing that effect.

Our fluorescein studies are really, at the moment, not comparable one photo to another. But our general impression, looking over serial fluorescein studies, it that we may be getting an improvement in the staining or leaking areas by treating other areas.

Dr. Welch: Concerning treatment of exudates in the macula, I started this because I noted that treatment of retinal aneurysms and altered vascular areas caused reabsorption of lipid. King, Dobree, and Dangerfield, when they used low animal fat diets, noted reabsorption of lipid, but commented that visual acuity did not improve. I don't find this to be the case. In fact, you can notice quite marked visual improvement in certain cases, and, therefore, I think it is rather important to treat the ideal case. In these respects, I certainly agree with Dr. Wessing. He has already showed how you can get reabsorption of lipid by discretely treating the area of aneurysms or the neovascular area. I would like to know whether Dr. Aiello has been able, through laser treatment, to decrease the metabolism of the retina and is able to get this change. At the USPHS hospital in Balitimore, they don't have a Zeiss photocoagulator but do have a laser. I prevailed upon them to treat a number of these areas with their laser, and they haven't been able to get this reabsorption.

Here is a case (fig. 1) with some early lipid formation in the macular area. This picture shows reabsorption of lipid. Remember, it takes a long time for lipid to be reabsorbed from the retina. As a matter of fact, it can take months.

This other photo (fig. 2) shows a marked area of circinate lipid and retinal edema. You see rather heavy lipid getting reabsorbed after photocoagulation. All patients do not improve to this dramatic level. Nevertheless, it certainly is worth treating the ideal cases.

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FIGURE 1.—*Circinate lipid complex. Left: Schematic drawing of circinate lipid complex involving macula; vision 10/200. Middle: After photocoagulation of aneurysms. Right: Complete reabsorption of lipid; vision improved to 20/40+.*

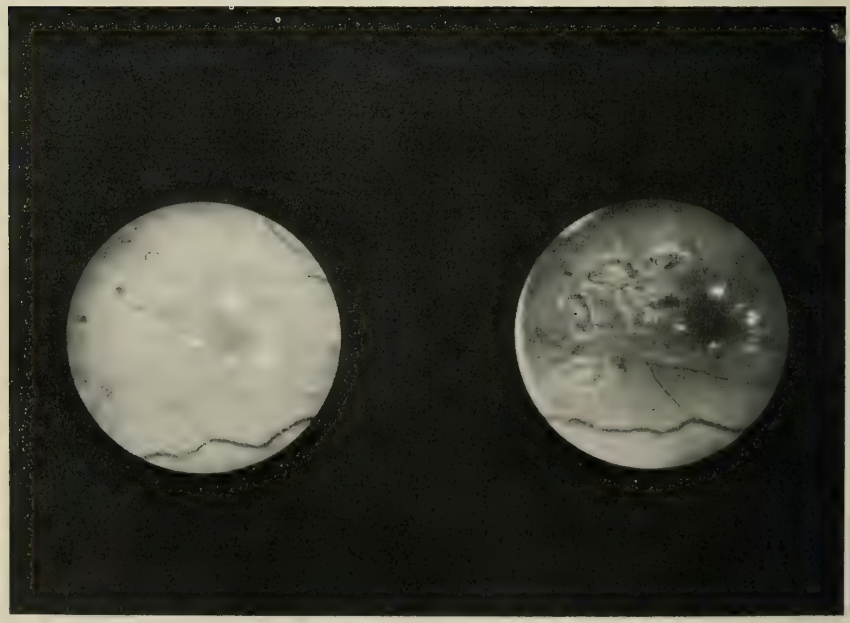

FIGURE 2.—*Circinate lipid. Left: Circinate lipid: many areas of leaking aneurysms. Right: Post-photocoagulation, lipid reabsorbing.*

There will be a question as to how many controls I have, and I don't have many controls. I do have some cases with circinate in the macula that I have followed, but I never saw it disappear like this through the natural history of the disease. I would be interested to know if others have seen this.

Dr. Wetzig: What is the time relationship between absorption of the lipid and improvement in vision?

Dr. Welch: In the case shown in figure 2, the initial vision was 20/400. In this particular case, the vision had improved to 20/100, in spite of residual lipid. It took about 9 months to get a complete reabsorption of lipid. Some of them don't take that long, but others do. Of the eight cases, all with areas of circinate, I reported here (Ch. 47), six do show improvement of vision.

Dr. Lundbaek: I want to suggest to you that it took about 15 years before it was realized that it was necessary to try the approach of clinical experiments in evaluating endocrine treatment and pituitary ablation. We have heard tonight very little about control. We have heard a lot about diversity of opinion. I would suggest that it would be right for you ophthalmologists to try to think a bit more about the design of an experiment.

Dr. Fraser: Several of us, perhaps physicians like myself, would very much like to have a little more than speculation about how photocoagulation in certain areas can influence the retina in other areas. It has been, of course, easy to see that burning an area where there are localized new vessels would alleviate or at least eliminate the new vessel formation in that area. Can anybody produce a case which has had a series of photocoagulations in which the intervening areas were altered as regards new vessels? It would be very interesting if we could have any documentation.

Dr. Okun: I have a feeling that people are getting the wrong idea about what is being done with photocoagulation today. Actually, all but one member of this panel treats directly at areas of neovascularization in attempting to obliterate these areas. Some people were confining their therapy to abnormal areas or areas of leakage, but were hoping to dry up other areas.

There really is only one group of investigators who are using this spray therapy, and they are the first to state that it is still experimental. It is being done because many people have observed that certain conditions are associated with amelioration of the diabetic retinopathy for some unknown reason. I don't think anybody knows why it happens. It just happens. It happens spontaneously.

Dr. Kohner: I would like to ask Dr. Welch whether the circinate retinopathy was not, in fact, macular edema? We have seen hard

exudates by themselves. It has been shown by several people that low fat or Atromid-S gives results which are just as good. Sometimes, it doesn't take 9 months. Has this been compared in any way?

Dr. Welch: The answer to both of those questions is: No. The patients had circinate retinopathy and edema of the macula within that circinate area.

Dr. Wetzig: There is a problem about the fate of the existing retina when these hard exudates clear, and we have some variations of opinion.

Mr. Dobree: There was one interesting thing about the series we did with the corn oil diet. Although the exudates initially disappeared, the visual acuity still remained low after about a year. But a lot of the patients were keen on the idea of corn oil, and thought they were doing good, and went on with it. Years later, we found several had regained quite a lot of vision.

Dr. Ray: When there is extensive destruction of areas of the retina for retinitis of this type, what does the patient say about his visual field defects? Does this really affect his vision significantly? Is he concerned about it?

Dr. McMeel: You get a field defect that is significant when you obliterate the nerve fiber layer. When the xenon arc lesion is moderately heavy, especially when you treat the rather specific neovascular lesions of the moderately advanced and the far advanced proliferations, you eliminate the field peripheral to your lesion.

Patients, however, will not have a subjective awareness of a field defect until you get within about 15° to 20° of the fixation point. This has been quite surprising to me. If a patient has one eye, of course, he is more apt to notice this. Even in the one-eyed patient, the defect still has to be within 15° or 20° before he notices it. Obviously, he will notice it a bit more if the field cut is temporal, but you can get away with even a more extensive field cut in the superior and nasal fields. If you are working on a two-eyed patient, this problem is even less. I have been somewhat reassured by literally dozens of patients in whom we have a significant constriction but no subjective complaint.

Dr. Wetzig: Following this extensive treatment, patients really are surprisingly unaware of loss of field. This is especially true if these burns are made small, which would certainly be an advantage with the laser. The same thing holds true for the light coagulator. If we make the burns small, as long as they are not confluent, these patients, as a rule, are not aware of a field loss. Of course we can map these out, but the practical thing is that the patient is unaware of them.

Dr. Beetham: This so-called bombardment of the retina with the laser does not produce any demonstrable field cut that we have been

aware of. We have attempted by all our office means (with the perimeter and three millimeter test object and with the tangent screen and 3/1,000 test object), but have not yet been able to demonstrate a scotoma. We don't deny there are field defects which should be elicited in some more refined manner.

That is exactly why we chose the laser—because we got no field defects. That is not the case with the xenon light coagulator. I have seen a good many of Dr. Wetzig's cases who have complained bitterly of field defects.

I think I can produce 50 patients who have been coagulated by the xenon arc with a great big field defect, but none with the laser.

Dr. Wetzig: Of course, we have two choices. Which will we prefer: central vision or malignant lesions adjacent to the macula which wipe out the macula? Of the two choices, I think most of us would prefer to retain our central vision.

Dr. Schimek: I would like to mention a somewhat different technique and philosophy of laser treatment that I have been using for a number of years. I had been a great deal more timid with the light coagulator than some others in producing chorioretinitic lesions. I continued this conservatism with the laser. During the past 4 years it has been my practice to bombard the area of pathology (be it microaneurysm, exudate, or new vessels) with multiple applications of the lightest possible reaction that can be produced by the laser. My feeling is that most of these problems could be observed for quite a period of time before having to rush ahead and put in heavy reaction. If you undertreat to the extent that you see no reaction, the next time the patient comes back, he can easily be retreated, because he doesn't have to undergo any retrobulbar injection.

It has been my impression that the one eye that I have treated (the worse eye in each patient) has fared much better than the fellow eye over the course of these last 4 years. This is without the heavy reactions that have been shown here. These have been a good deal lighter than the laser applications that we were shown by Dr. Aiello and lighter than the xenon scars shown previously.

Dr. Wetzig: Dr. Spalter, I believe, has experience with both xenon coagulator and the laser. I would like to hear his comments on which he prefers.

Dr. Spalter: I think that the key to much of our therapeutic armamentarium is the operator. Any ophthalmologist who is well qualified and equipped and who is trained in the use of either instrument certainly can do the job, based on his own rationale, that he sets out for himself. It is certainly conceivable that it is much easier to destroy large areas of retina with the laser. No anesthesia is required.

There is probably a slightly lower incidence of complications because of the quality of the laser beam and its lack of damage to large blood vessels.

On the other hand when we are treating specific lesions, I think the xenon arc coagulator obviously has more of a specific indication because of its broad spectrum wavelength. In addition to these two techniques of light energy, if one is indeed trying to reduce total retinal volume, then one can add the cryoprobe (at $-70°$), which, in the periphery of the retina, is quite safe to use. Dr. Campbell at Columbia and I have done a few cases, in which the thesis is: Let's reduce retinal volume and reduce metabolic demands. Granted we don't precisely know in what direction we are going, but this concept is at least entertaining as an approach, and it is a very simple way to destroy a great deal of peripheral, nonvital retina without complications.

Dr. Zweng: We can speak from experience that embraces over 300 patients treated with laser photocoagulation for a variety of retinal diseases, and in none has there been demonstrable a nerve-fiber-type field defect.

In macular disease, with experience in over 100 cases, where there has been treatment directed to a leak demonstrated with fluorescein, one can pick up a very tiny scotoma. The patient is generally unaware of this, since he is seeing very much better than he did pretreatment. This is a very striking fact, and can be obtained with xenon arc photocoagulation if the amount of energy put in is very low.

Mr. Dobree: I agree that you simply do not get sector defects. In an accidental macular burn, the field defect is a scotoma and exactly matches the burn.

Dr. Duane: I know certain people have said they don't get visual field changes with therapy, particularly the Boston group. We do find visual field changes.

Dr. McMeel: It seems to me that the laser people are treating colds and we are treating pneumonia. In other words, the people using the laser are definitely treating at an earlier phase of the disease. They are treating very few, if any, who have any significant degree of vitreous hemorrhage. They are treating few, if any, who have a large series of these vascular fans that Dr. Okun showed or that I showed earlier today where we use relatively strong treatment.

In essence, we are treating two different phases of the disease. It is somewhat like the retinopathy classification. There is background retinopathy and there is proliferative retinopathy. Although the laser people are treating a phase of the proliferative retinopathy, it is nonetheless an early phase of retinopathy. I think Drs. Balodimos and Beetham would agree to that.

Hopefully, maybe we can educate the general physician to get the patients in to us at this early stage. This is an imperfect world, and most of us are not seeing these patients until they have the more advanced phases of the disease.

Dr. Wetzig: It has been mentioned that the use of intravenous fluorescein prior to treatment is of value in deciding where to treat. There have been some people who feel that it is an adjunct in treatment in that it absorbs heat. I would like to inquire of the panel what strength fluorescein they use and how much.

Dr. Okun: Ten milliliters of 5 percent fluorescein.

Dr. Zweng: So do I.

Dr. Wetzig: We recently have been using 10 milliliters of 10 percent fluorescein, and it improves the quality of the photographs and pools the dye more effectively. It is quite a striking difference. We had no ill effects from it.

Dr. Spalter: I think it was Dr. Wetzig who called to our attention the fact the fluorescein, as will many dyes, absorbs xenon arc energy. Usually we depend on the pigment of the pigment epithelium to absorb light energy. When dealing with so called avascular fibrous bands elevated above the level of the pigment epithelium, one might say: What is the point of treating it? But with fluorescein studies, very faint filling may appear. Something had to enter that "avascular" band. Therefore, Dr. Wetzig's point that we pool fluorescein there and get more absorption of photocoagulation energy is well taken. However, in practice, I have not found it to be terribly effective, because the amount of energy absorption is not sufficient to duplicate the same set of circumstances as when the pathologic lesion is on the surface of the retina. On one or two occasions, some sort of blanching of this type of elevated tissue, some decrease in vascularity, seems to occur, but it seems to regain its status after a few minutes go by, despite large doses of fluorescein.

We have treated one patient on the disc and surrounding the disc. We had a large field defect because of it, and we were rather discouraged.

Dr. Wetzig: I would like to ask Dr. Wessing two questions. First, how often should treatment be given? Second, how often should the followup visits be?

Dr. Wessing: In treating early cases, 200 to 300 coagulations are enough. These can be applied in one session. In advanced cases, it seems better to do coagulations in two or three sessions. Followup should be immediately after the coagulation, 4 weeks later, and 2 to 3 months after that.

Dr. Field: What interfaces, if any, exist between this form of attack

on diabetic retinopathy and pituitary ablation? Secondly, is there any actual evidence that the metabolism of the retina has, indeed, been changed? If it has, in what direction? Is it increased or decreased? Is the substrate different? Is there any information at all about this speculation?

Dr. Roth: We use both light coagulation and cryohypophysectomy as complementary forms of therapy at UCLA, and feel that one is not necessarily independent of the other. Rather, there is a specific time for each, with a grey zone between the two therapies. There, the choice becomes somewhat difficult.

It seems most of the ophthalmologists tend to treat the early cases of proliferative retinopathy. When this begins to advance, with more generalized, enlarged hemorrhages, consideration of pituitary surgery then begins to take over in my mind.

When we are dealing with the patient with only one eye, I may choose to treat that eye initially with a bout of light coagulation, but, if the patient begins to hemorrhage again, then I begin to become more concerned about the complications of additional light coagulation and begin to consider cryohypophysectomy.

Dr. Wetzig: What complications were you anticipating?

Dr. Roth: Retinal detachment from additional light coagulation is probably my biggest concern, as well as provoking additional hemorrhage.

Dr. McMeel: The ideal for photocoagulation should include clear media, discrete lesions, flat lesions, peripheral lesions, and primarily vascular lesions with very little, if any, fibrotic proliferation. Once you start getting away from this ideal, if your lesions are no longer discrete but are massive, if they are vascular fans that tend to come out into the vitreous, if they are central rather than peripheral, and if they have a certain amount of fibrotic overgrowth in addition to the vascularity, you have conditions that make one more apt to use pituitary ablation instead of photocoagulation. I don't think you can say where the cutoff point in any one case is.

Also, if you have a diffuse vitreous hemorrhage through which you cannot see a specific bleeding site, this may be another factor that would decrease your chance of doing a successful photocoagulation.

Dr. Field: What about photocoagulation after hypophysectomy?

Dr. McMeel: It certainly is done, and, as Dr. Roth intimated, these two should be used together. There are cases who had photocoagulation performed first (with subsequent pituitary ablation) and others who had ablation with subsequent photocoagulation.

We have used photocoagulation after hypophysectomy in those instances where there has been a persistence of dangerous vessels or

a recurrent hemorrhage from one small area after pituitary ablation. Everything else may have simmered down except for two or three relatively localized areas.

There is also a group in which we might have advised pituitary ablation, but, because of their medical situation, their age, or their psychologic makeup, one would not do pituitary ablation. In those, we would go ahead with photocoagulation with the understanding that our chances for cure would not be as good as if pituitary ablation were used.

Also, there is a group of patients in whom there is a mixture of fibrotic retinopathy and vascular retinopathy. I think we are all aware that if there is too much fibrotic retinopathy you can have a secondary detachment. In a certain few of these cases, it may be worthwhile to use photocoagulation in well selected instances.

Dr. Thornfeldt: We all have to remember that we have a patient who has proliferative disease. He does not have too long to live, whether we coagulate him or ablate him. We have to do the least damaging procedure to him. It has been my impression, after listening to this symposium and from my own experience, that if we are going to treat, we have to do it early. We can't take the ablator's problems, the ones he hasn't been successful with, and expect to get anything out of it, nor can he take our problems.

Dr. Oakley: The fact is that ablation of the pituitary has a systemic effect on the patient with diabetes. Generally, we have been reluctant to do it, therefore, until the patient has spectacular retinopathy, often with fibrous tissue extending toward the vitreous.

The fact is that our best results have been obtained on patients with extensive new vessels on the surface of the retina, often with 20/20 vision in both eyes. I think this is the same group that does well with photocoagulation.

To say that one phase is suitable for photocoagulation and another phase is suitable for pituitary ablation is really letting ourselves into a degree of simplicity that doesn't exist. I think it is a street fight over the same ground. The same patients are best photocoagulated as are ablated, and if the photocoagulators can convince us that they can get as good results as we get without what are, in fact, damaging effects to the patient's general medical health, we will concede victory to photocoagulation. As we stated with respect to controls, we have to get the facts from photocoagulation as well as the facts from pituitary ablation.

Dr. Joplin: It is possible for anyone using photocoagulation to give us some figures on the effect of their operation on the frequency of vitreous hemorrhages?

Dr. Okun: Unfortunately, this is one parameter that was not mentioned in the papers I reviewed. The thing that is mentioned is whether at the time of last examination, there was hemorrhage in the vitreous. It is well appreciated in each of the papers that, if you are starting with a hemorrhagic condition in the vitreous, the prognosis is not nearly as good as when starting before there is hemorrhage in the vitreous. The major reason for vitreous hemorrhage is traction on areas of neovascularization. Unfortunately, neither photocoagulation nor pituitary ablation does a great deal for the traction. I do feel that even in some traction hemorrhage cases (and this is where I take issue with other members of this panel) I have been quite successful in completely eliminating that hemorrhage and not having any further recurrences of hemorrhagic activity for followup periods of 2 to 5 years. This certainly isn't true in every case. There are some cases in which I treat a hemorrhage and then, 4 or 5 weeks later, there will be another hemorrhage from another area, indicating that there has been further traction of the vitreous from either the previous treatment or from the effect of blood on the vitreous membranes, which causes them to shrink.

How to handle the traction-type hemorrhages? Sometimes, as Dr. Wessing has shown, there is absolutely no question that you can just obliterate that whole area. In others the membrane and vitreous may detach completely from the retina, and you are left with an excellent result. This doesn't happen every time.

Dr. Knowles: I read carefully all of the reports on photocoagulation, and I couldn't, in my own mind, really get a view as to just how many patients were benefited, when, or how long after treatment? When we have patients followed for varying times, this information cannot be compared between groups. All of you have very good prospective data. You started treatment at time zero. All of these articles have beautiful tables showing the course of every patient. I would like to make a plea for the development of an actuarial or life table type of statistical system in plotting what happens to your patients, so that you can compare your results with each other.

Dr. Lundbaek has asked for experimental design with controls and so on. I would just like to plead for a good means of plotting your data so that we, who are in the internal medicine world, can read your papers and get a view of just what the natural course of events is after treatment.

Dr. Wetzig: I think you are quite right, Dr. Knowles. This is the purpose of trying to get a standard classification so that we have something to compare.

Dr. Davis: I am going to agree with what Dr. Knowles said.

Dr. Norton: As an ophthalmologist sitting out here among internists and neurosurgeons who are squirming in their seats and trying to figure out what is going on (we have for example, Dr. Field asking, "What evidence is there that something happens to the retinal metabolism?"), I get a little disturbed, particularly since we heard all the material on hypophysectomy. I want to tell Dr. Field we will answer his question when he tells me how hypophysectomy cures diabetic retinopathy.

Dr. Duane: I think it is the relationship of intraretinal arterial pressure and intraocular pressure that is of primary importance in what goes on in these diabetic retinas.

In some cases of symmetrical diabetic retinopathy, where there is a difference in the degree of retinopathy on one side and the other, if one has unilateral glaucoma, the eye with the glaucoma has a lesser degree of retinopathy, which is probably a poor trade. Something happens between the intraretinal and intraocular pressure; the closer these come together, the better for the diabetic retinopathy.

The same is true in ocular hypotony, such as occurs in the immediate postoperative period following cataract surgery. Everybody knows if you remove a cataract from a patient, the likelihood is that retinopathy is going to become greatly aggravated in the postoperative period. If one has arterial hypotension, the diabetic retinopathy will very often be greatly ameliorated. This occurs in artery disease, central retinal artery occlusion, and in other retinal involvement which becomes superimposed on the diabetic retinopathy. This is germane, because, if we are really going to evaluate these patients, particularly in a prospective way, it is very important that we measure intraretinal arterial pressures. Of course, it comes down to a matter of practicality. It is extremely difficult to do all the tests involved. The photographic people don't want us to put a contact lens on the eye. We give fluorescein, and there seems to be interference with some of their studies. These patients then have to stay around a couple of days to be reevaluated. They don't like it; it costs them money. On the other hand, in photocoagulation studies, when you talk about comparing one eye to the other or using one eye as a control, if you haven't measured the intraretinal arterial pressure, you don't know these two eyes are equal, even though they may look the same. We have to measure these arterial pressures if we are going to know if our treatment is improving the diabetic retinopathy or not.

I get very upset when I hear about people talking about changing the metabolism of the retina, because I don't think we have any way of getting at the metabolism in the retina of the patient on the hoof, or the capillary pressure or venous pressure either.

When I first started looking at these diabetic patients in great numbers, I really was highly skeptical that any form of therapy made any great difference. The one thing I have been able to convince myself of, from the work of Dr. Field, is that pituitary ablation does result in positive signs that can be measured. The clearing of the vitreous immediately after surgical ablation, regardless of what causes it, is an objective sign. I also think that the disappearance of the vascularity in fibrous bands, particularly those bands coming off the disc, is another objective sign.

What is going on with photocoagulation is chaotic. I looked at some of these slides, and every one where the disc could be seen shows some atrophy. If you tell me you can eliminate retinitis with a laser, and you don't get any visual field changes, then something is awfully different about retinitis as it occurs in Boston compared with Philadelphia, because we get all sorts of changes.

Dr. Okun: With regard to Dr. Duane's extremely provocative talk, I might ask Dr. Duane how he proposes to reduce the retinal arterial pressure and whether he measures it all the time and has been doing so right along. I might ask whether he feels he is capable of measuring retinal arterial pressure aside from the pressure which might exist in the ophthalmic artery. I would also like to know what other studies are going on at the present time at his institution. We also feel that optic atrophy is important, as noted in our publication, because we feel we are producing some. We would be willing to accept it, as long as we keep visual acuity in good shape.

Dr. Davis: I am sure Dr. Duane will submit such data to us through the regular channels.

Dr. Wetzig: We are going to poll the audience. The question is: If you, yourself, had diabetic retinopathy in a progressive angiopathic state, with early neovascularization and little or no fibrosis, good visual acuity, and if you were in a state of fairly good general health, would you choose to (1) permit nature to take its course, hoping that an arrested or more quiescent stage would be reached before total blindness occurred; (2) Would you choose to be treated by photocoagulation? or (3) Would you choose pituitary ablation?

Who would sit and let nature take its course? Seven people.

Would you choose to be treated by pituitary ablation? Roughly 10 or 11.

Would you choose to be treated by photocoagulation? Majority.

Dr. Kohner: I would have pituitary ablation, yes, but only if an ophthalmologist first looked at my eyes to decide what type of lesions I had; only if physicians (preferably from the Hammersmith Hospital) looked at my diabetes; and only if Dr. Hardy would do my pituitary ablation.

Dr. Bradley: I think that it would only be fair for Dr. Wetzig to ask the question giving a different retinal classification with a little more severe disease; for example, N_2 F_2 H_2, the hemorrhage being recent.[1]

Dr. Lundbaek: I have another suggestion. I would be very pleased to enter as a volunteer in a group to be treated with photocoagulation with laser or without laser, in a control group or in a treated group, if such groups would only exist.

Dr. Greenberg: Much of what has been presented is like locking the door after the thief had been there. Maybe some thought should be given as to the earliest manifestations of diabetic retinopathy. Maybe fluorescein can give us some answers. Surveys as those for the detection of diabetes should be going on. Similarly, should we treat diabetic retinopathy where we don't see microaneurysms. Will fluorescein show aneurysms which are not clinically apparent?

Dr. Linfoot: I would like to ask Dr. Davis a question. Am I safe when I go home to state that all methods of therapy that are currently being employed in the treatment of diabetic retinopathy remain experimental? Can I still say that to a patient?

Dr. Davis: I don't think we can get a unanimous answer from the group. I would hope it is still experimental in the way you look at it. Maybe the patient won't look at it that way.

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[1] O'Hare Classification, p. xxi.

PART VI

Miscellaneous Topics

CHAPTER 53

Net Vascular Pressure Ratios in Diabetic Retinopathy

THOMAS D. DUANE, M.D.
THOMAS BEHRENDT, M.D.
RICHARD A. FIELD, M.D.

Relationships between intra- and extra-vascular pressures in the eye exert a major influence in retinal circulatory dynamics. During the last hundred years it has become increasingly apparent that the altered metabolic effects produced by diabetes mellitus in the eye has a predilection for expressing itself morphologically in the retinal tissues, particularly in the blood vessels. This in turn alters retinal structures in a manner culminating in a form which ultimately is recognized ophthalmoscopically and microscopically as diabetic retinopathy.

It is to the dynamic aspects of the retinal circulation that this paper wishes to draw attention and to relate theoretical considerations to basic and clinical observations. From this background, various methods which may elucidate mechanisms of deleterious and beneficial changes that occur in various forms of the retinopathy are suggested.

NET VASCULAR PRESSURE CONCEPT

The ophthalmic artery is a direct branch of the internal carotid. The central retinal artery and the short ciliary arteries are major direct extensions of the ophthalmic artery. Measurement of ophthalmic artery pressure is a standard procedure with the ophthalmodynamometer. Once blood enters the eye there is an alteration between the intra- and extra-vascular pressures. For purposes of discussion, the normal intra-retinal arteriolar pressure is assumed to be 75 mm. Hg. with full appreciation of how this pressure may vary even in a healthy individual as a result of changes in posture and other physiologic alterations which may occur in the cardiovascular system. The normal intraocular venous pressure is arbitrarily assigned a value of 25 mm. Hg. Normal intraocular pressure, for these purposes, is assumed to be 15 mm. Hg.

Jefferson Medical College of Philadelphia, Philadelphia, Pa.

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Hence, between the inside and outside of a normal retinal arteriole (and excluding tissue turgidity) there exists a probable pressure differential of 60 mm. Hg.: Intra-arterial pressure (IAP) 75 mm. Hg. minus intraocular pressure (IOP) 15 mm. Hg.=60 mm. Hg.

The ratio between the two, IAP/IOP, or 75/15=5, which is the index of the net vascular pressure.

It is our thesis that in diabetic retinopathy the higher the difference between these pressures, or stated another way, the greater the net vascular pressure ratio (IAP/IOP), the more deleterious changes in the retina may be expected.

Some examples are presented below:

Glaucoma

Becker (*1*) has summarized his observations and those recorded in the literature with regard to effects of changes in the intraocular pressure on the course of diabetic retinopathy. The evidence indicates beneficial effects of increased intraocular pressure on diabetic retinopathy. In other words, the lower the net vascular pressure ratio, the less likelihood for rapid progression of the retinopathy. Typical findings in a diabetic patient with coincidental glaucoma would be as follows:

Better (glaucomatous) eye, IAP/IOP, 75/40. Net vascular pressure ratio: approximately 2.

Poorer eye, IAP/IOP, 75/15. Net vascular pressure ratio: approximately 5.

Of course the terms "better and poorer" must be accepted in context and here refer to the changes in the diabetic retinopathy process. Philosophically it can be debated whether one suffering from one form of retinal disease can be assumed to benefit by contracting another. Indeed, many proposed forms of treatment for diabetic retinopathy seem to trade one form of retinal disease for another. Such trades may be beneficial, but they must be appreciated and weighed before advocated. The reversible increased intraocular pressure effects resulting from locally applied steroids makes this form of proposed therapy highly desirable when applicable and effective.

Ocular hypotony

The converse of glaucomatous changes, namely, reduction of intraocular pressure below normal, is widely accepted as exerting a deleterious influence on the evolution of diabetic retinopathy (*2*). A typical clinical example of this phenomenon occurs following cataract surgery which notoriously has been recognized as producing a worsening effect

on preexisting diabetic retinopathy. Here the hypothetical measurements are:

Better (nonoperated, phakic) eye, IAP/IOP, 75/15. Net vascu-pressure ratio: 5.

Poorer (operated, aphakic) eye, IAP/IOP, 75/5. Net vascular pressure ratio: 15.

Admittedly intraocular pressure does not remain hypotonic indefinitely in such patients, but it does exist for several weeks or more. It is precisely in this period when retinal deterioration is clinically observed. Most surgeons, with reason, are loathe to advise or perform cataract surgery in the presence of proliferating diabetic retinopathy.

Retinal arterial hypertension

Systemic hypertension is known to aggravate diabetic retinopathy (*3*, *4*). Gay has measured ophthalmodynametric pressures in patients with unequal degrees of diabetic retinopathy (*5*). He has clearly demonstrated that the differential is greatest in those retinas with diabetic proliferating retinopathy. Typical readings are:

Better (diabetic retinopathy without proliferation) eye, IAP/IOP, 75/15. Net vascular pressure ratio: 5.

Poorer (diabetic proliferating retinopathy) eye, IAP/IOP, 90/15. Net vascular pressure ratio: 6.

Ophthalmodynametric measurements are not easy to record in the presence of proliferating diabetic retinopathy for several reasons. First, the investigator must arbitrarily decide which tuft of vessels he will choose for observation of the end point; hence, his observations may be biased. Secondly, neovascularization vessels do not collapse simultaneously with any given elevation of intraocular pressure. Thirdly, ophthalmodynamometry is classically recorded by noting vessel changes at the disc. Proliferative retinopathy characteristically arises from the papilla, often precluding observation of this area. Finally, some observers are even hesitant to perform ophthalmodynamometry in the presence of proliferating retinopathy for fear of rupturing the poorly supported vessels during the procedure.

Retinal arteriolar hypotension

Many forms of vascular retinopathy improve with diminished intra-arterial pressure. When this is a systemic condition both eyes improve; indeed, the typical Sheehan syndrome displays marked hypotension (*6*), and this was true in Poulsen's original patient (*7*). Certainly in asymmetric retinopathy one frequently finds diminished carotid cir-

culation on the homologous side with the lesser pathologic changes. An extreme degree of asymmetry occurs in central retinal artery occlusion where diabetic retinopathy may completely disappear (*8*). Theoretical measurements would be:

Better (central retinal artery occluded) eye, IAP/IOP, 30/15. Net vascular pressure ratio: 2.

Poorer (nonoccluded) eye, IAP/IOP, 75/15. Net vascular pressure ratio: 5.

Again, "poorer and better" refer to diabetic retinopathy. Again also, there is a trade between one form of retinopathy with another which, in such an extreme instance, offers little to choose.

DISCUSSION

Pressure measurements in diabetic eyes with asymmetric degrees of retinopathy as presented above are summarized in table 1.

In health there appears a marked net vascular pressure ratio in the retinal vasculature. Normal values are in the range of 75/15 for a difference of 60 mm. Hg. between the intravascular and extravascular pressures. This is equivalent to a ratio of 5 and seems to be consistent with normal functions of the retinal capillary system.

When diabetic retinopathy intervenes, this normal differential seems to operate to the detriment of the retinal state. Under these conditions, it is assumed that increased pressures may be extended to the capillaries and veins. Further, it appears that lessening the differential (as measured in the arterioles) augurs well for slowing or abolishing diabetic retinopathy.

One wonders why or how this comes about. Little is known about the effect of raised or lowered vascular pressures on retinal capillary

TABLE 1.—*Asymmetrical diabetic retinopathy*

Complicating factor	Poorer eye [1]			Better eye [1]		
	IAP/IOP	Difference (mm. Hg.)	Net vascular pressure ratio	IAP/IOP	Difference (mm. Hg.)	Net vascular pressure ratio
Glaucoma (unilateral)	75/15	60	5	75/40	35	[2] 2
Ocular hypotony (intraocular surgery)	75/5	70	15	75/15	60	5
Arteriolar hypertension (asymmetric diabetic proliferating retinopathy)	90/15	75	6	75/15	60	5
Arteriolar hypotension (central retinal artery occlusion)	75/15	60	5	30/15	15	[2] 2

[1] "Poorer" and "better" refer to degree of diabetic retinopathy. See text.
[2] Approximately.

physiology in health or disease (*8*). All that can be stated is that once diabetic retinopathy has appeared, the more equal the intra-arterial pressure and the intraocular pressure, the less severe will be further development and progression of the retinopathy.

This has a direct bearing on therapy. With regard to vascular pressures the therapist has two choices, either to raise the intraocular pressure or to lower the intra-arterial pressure.

Raising the intraocular pressure is clinically impractical with the exception of those individuals who react positively to steroids which, fortunately, may have a common genetic basis with the incidence of diabetic retinopathy as pointed out by Becker (*1*). Excessive reduction of intraocular pressure can be avoided by foregoing intraocular surgery.

Lowering of intra-arterial pressure occurs frequently in nature (carotid artery disease, systemic hypotension, central retinal artery occlusion) and has a beneficial effect on diabetic retinopathy. This is not a panacea, however. To date, clinical production of deliberate unilateral hypotension defies clinical capabilities. It is possible to gradually occlude the carotid artery. This is a dangerous procedure in the diabetic patient with cerebrovascular disease which, unfortunately, often is the case in diabetes. It is impossible to partially occlude the ophthalmic artery clinically.

There is evidence that central retinal artery embarrassment occurs secondary to optic atrophy. It has been postulated that this may be the mechanism of the beneficial effects resulting from extensive photocoagulation treatment of diabetic retinopathy. If enough of the ganglion cells are destroyed, optic atrophy becomes manifest. Whether the treatment is better than the disease is not clear. As mentioned above, trading retinopathies does not offer much of a choice to the patient.

It would be pleasant to report that effective hypophysectomy produces consistent systemic hypotension. Although this occurs in the classical untreated Sheehan's syndrome, it has not been the experience in our series of patients with pituitary ablation. Further, many patients displaying progressive diabetic retinopathy do not suffer from systemic hypertension.

At present we have under consideration a theory which will explain the pathogenesis of diabetic retinopathy, taking into account the metabolic and vascular changes known to be present. It is premature to offer this theory at the present time. The final effect, however, is known to be an increased head of vascular pressure and rate of flow to the retinal capillaries and venules. As a result, there is an increase in the net vascular pressure primarily on the venous side of the capillary network (see table 2).

TABLE 2.—*Arteriolar versus venular pressures*

	Arteriolar side			Venous side		
	IAP/IOP	Differential (mm. Hg.)	Net vascular ratio	IVP/IOP	Differential (mm. Hg.)	Net vascular ratio
Normal	75/15	60	5	25/15	10	1.66
Diabetic Retinopathy		Same		45/15	30	3

If these speculations are valid, then the events listed in table 1 would obviously either aggravate or improve the abnormal flow in the capillaries on the basis of how the pressure relationships between the inside and outside of the vessels were modified. In order to bring some light to these speculations, it is recommended that several clinical studies be pursued. They are as follows:

Pressure measurements

Repeated measurements of intra-arteriolar pressure and intraocular pressure should be made on all patients with diabetic retinopathy. These should be made especially before and after instituting such therapeutic measures as diet, drugs, photocoagulation, and hypophysectomy. Of course, it is additionally recommended that careful records of systemic blood pressures be maintained.

It must be recalled that ophthalmodynamometry measures pressures in the ophthalmic artery, not in the retinal. When the ophthalmic artery pressure is low, it is obvious that the pressure downstream (in the retinal circulation) must be correspondingly low or lower. The converse is not true. Pressures may be elevated in the ophthalmic vessels but normal or low in the retinal vessels due to local, possibly compensatory, changes in the latter. This indicates the need to discover methods to measure retinal vascular pressures. Desired are methods to measure arteriolar, capillary, and venular pressures.

Fluorescein times

As suggested by Norton and Gutman (*9*), the rate of flow of flourescein through the retinal vasculature is now available to quantitative analysis. Patients demonstrating the various stages of diabetic retinopathy should be evaluated as to (*a*) total retinal circulation time, and (*b*) venous circulation time. These measurements should be correlated with therapeutic interventions, particularly those resulting from photocoagulation and hypophysectomy. In the interest of making such measurements relevant, they should be related to similar studies in normal, healthy individuals.

Again a word of caution before one takes circulation times as indicative of retinal vascular flow. All that has really been measured to date is circulation time. Little or nothing is known about retinal velocity which involves fixed distances (i.e., including observation of shunts, neovascularizations, rete, etc.). Still less is known of perfusion rates which further involves diameter of vessels, their shape and viscosity, as well as pressure and how these vary with disease.

When careful quantitative facts from such studies are in hand, it may be possible to make a more meaningful theory of the pathogenesis of diabetic retinopathy; and possibly some day there will evolve suggested avenues for clinical alterations of the more clearly understood abnormal conditions existing in the diabetic retina.

SUMMARY

The concept of net vascular pressure ratio is presented. This refers to an index of the difference between intraretinal arteriolar pressure and intraocular pressure. When the ratio is low as occurs in arterial hypotension and glaucoma, there exists a beneficial effect on diabetic retinopathy. When the ratio is high as in systemic hypertension and ocular hypotony, a deleterious effect occurs in diabetic retinopathy. The theoretical implications of these observations are discussed and suggestions for further observations are presented.

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CHAPTER 54

Effect of the Ruby Laser on the Monkey Retina: An Electron Microscopic Study (Addendum to Paper by Aiello et al.)

TOICHIRO KUWABARA, M.D.
LLOYD M. AIELLO, M.D.

In order to determine the direct effect of the ruby laser burn on retinal tissue, animal experiments using normal monkeys were carried out in a manner similar to human treatment. The retinal tissues of the animals were examined electron microscopically. Also, the vascular pattern of the treated retina was studied by means of the trypsin digestion technique.

MATERIAL AND METHOD

Normal young rhesus monkeys were anesthetized by sodium pentobarbital, and their pupils were dilated with 10 percent neosynephrin and 1 percent mydriacyl. The American Optical pulsed ruby laser photocoagulator (6343A°) was used to produce 2.5 degree (0.75 mm) lesions. The power setting was calibrated to produce grade I, II and/or III and IV clinical lesions. Approximately 150 to 200 lesions were made in the posterior pole of each monkey retina, sparing the disc, papillomacular bundle, and the macula, and leaving a small interval of normal retina between each application. This technique duplicated that carried out on patients with diabetic proliferating retinopathy presented in the foregoing report (*1*).

Animals were killed at time periods of 2 days, 2 weeks, 1, 2, and 3 months after treatment. One monkey was treated twice, the second treatment taking place a month after the first, and was examined 2 months after the second treatment.

The whole posterior half of the excised eye was fixed in 4 percent glutaraldehyde solution in pH 7.2 phosphate buffer. During the 20 minute fixation in the glutaraldehyde, the tissue was examined under a dissecting microscope and small pieces of the treated areas were care-

Howe Laboratory of Ophthalmology, Harvard Medical School and the Diabetes Foundation, Inc., The New England Deaconess Hospital, Boston, Mass.

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fully dissected. At least 10 locations from each retina were examined. The small pieces of the retina were embedded in epoxy resin. Sections were examined by electron microscopy.

Portions of the retinas were studied histologically and the blood vessels in both treated and adjacent areas were examined by the trypsin digestion technique (*2*).

RESULTS

At the moment of the application of the laser beam the pigment epithelium "boiled" briefly and the area became a grayish white patch a quarter of the disc in size. The spots stayed without appreciable change in size or appearance for about 1 month. About one-half of these spots gradually faded out in about 3 months, and the rest remained for more than 4 months. No hemorrhage or intraocular inflammation was noted in the regularly treated retina. Some spots were outlined by light pigmentation. A few severely damaged foci (grade IV burn in which small hemorrhage was noted at the time of the exposure) became discrete white spots. These spots were often circled by a considerable amount of heavy pigmentation.

Early Stage

Extensive cellular destruction was demonstrated in the photoreceptor and pigment cells immediately after the laser exposure. However, the damage was noted to be sharply localized in a small area. The severest damage appeared to occur in the pigment cell layer. The cytoplasm of the pigment cell was profoundly vacuolated and all micro-organelles were destroyed. Because of the sharp discrete burn, normal cells were often found directly next to the severly damaged ones.

On the second day the burned area became markedly degenerative. Pyknotic and fragmented nuclei were found to be abundant in the outer nuclear layer, and the photoreceptor segments were markedly fragmented (figs. 1, 2). Several pigment cells (average of 10 cells were seen in a center section of the burned spot) showed total necrosis. The adjacent normal, or partially damaged pigment cells started to show prompt reparative reaction, i.e., enlarged endoplasmic reticulum and an increased number of lysosomes (fig. 3). The subretinal fluid contained fibrin and various cell debris (figs. 2, 4). The photoreceptor outer segments in the damaged area showed marked irregularity of the lamellar membrane, but no vacuolar or tubular transformation which was common in light damage (*3*) was demonstrated (fig. 4). Bruch's

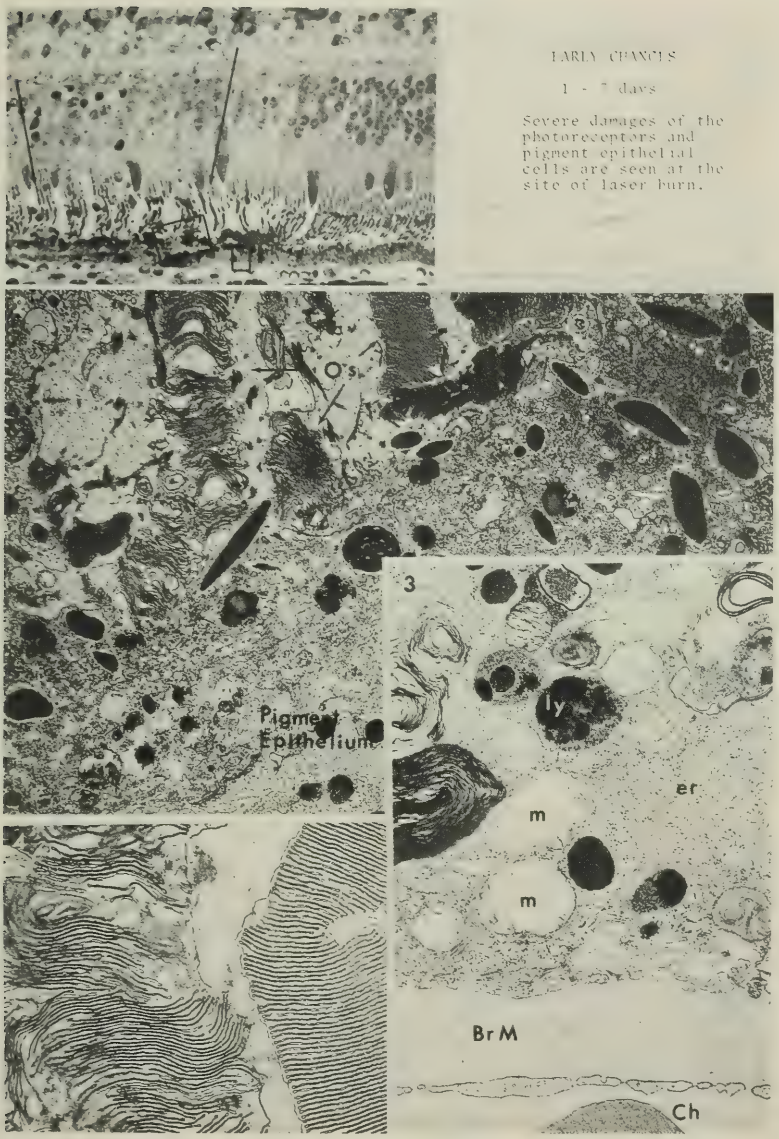


FIGURE 1.—*Two days after the exposure. Arrows indicate the focused area. Pyknotic nuclei are seen in the outer nuclear layer.*

FIGURE 2.—*Exposed area 2 days after the burn. The outer segments (Os) are fragmented. Microvilli of the pigment cell are seen in the center lower portion.*

FIGURE 3.—*The pigment cell directly adjacent to the exposed area shows enlarged endoplasmic reticulum (er), numerous lysosomes (ly), swollen mitochondria (m), and lamellar substance. BrM: Bruch's membrane, Ch: choroidal vessel.*

FIGURE 4.—*Photoreceptor outer segments show irregular arrangement of the lamellar membrane.*

membrane and the choroidal vessels seemed to be intact. No appreciable changes in the blood vessels and the vascular pattern were noted in this stage.

Recovery Stage

It was remarkable to find that the degenerated tissue had been cleaned out within a short period of time. Necrotic substances were totally absent in the damaged area in 2 weeks (fig. 5). Electron microscopically, the pigment cells in the damaged area (center of the whitish spot) showed a few vacuoles, apically located melanin granules, increased number of lysosomes, and elongated mitochondria (fig. 6). The outer segments appeared to be normal with respect to size and the lamellar arrangement of the membranes. Only a few fragments of cell debris were found in the subretinal space.

Blood vessels found in the burned spots showed small and localized pathological changes. The damaged capillaries appeared to be obliterated and formed small clusters or strands (fig. 7). They were surrounded by normal capillaries, and the general vascular pattern was not altered.

Except for the increased number and size of lysosomes in the pigment cells (fig. 8), histological appearance of the retina at the burned area became totally indistinguishable from normal in 4 weeks.

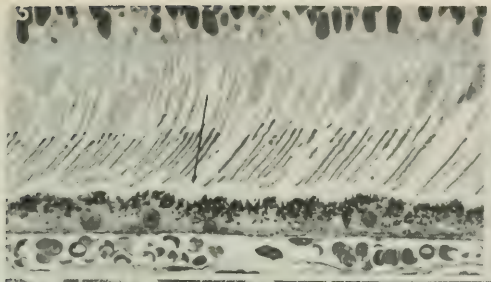
Late Stage

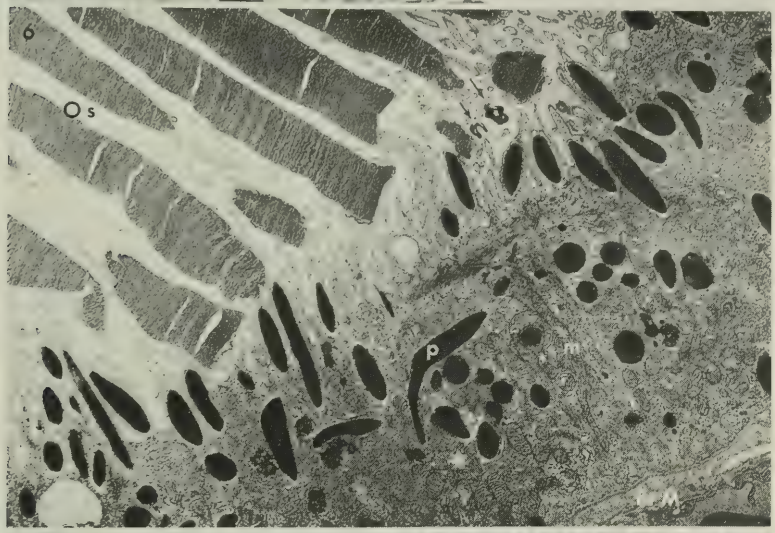
Only the severely damaged retina showed pathological findings after 4 weeks. In some foci which had been damaged by stronger beams, small photoreceptor outer segments were forming in the proliferated microvilli of the pigment cells (figs. 9, 10). The most severely damaged areas, which became discrete white spots, showed firm adhesion between the retina and Bruch's membrane. These areas appeared to fail to regenerate the pigment cells (figs. 11, 12).

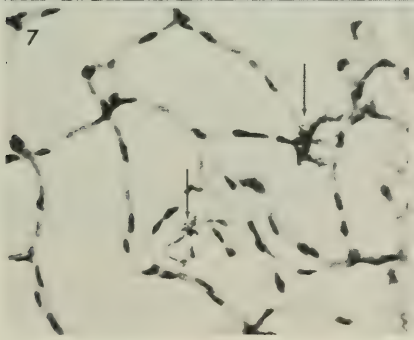
Blood vessels in the scarred area became a cluster of fibrous strands. The vasculature of the rest of the retina showed normal pattern and cytology. Occasional acellular strands were the only pathological findings in this stage (fig. 13).

COMMENT AND SUMMARY

This experiment demonstrated that the ruby laser caused a sharply localized damage in the retina. Burned and degenerated retinal tissue







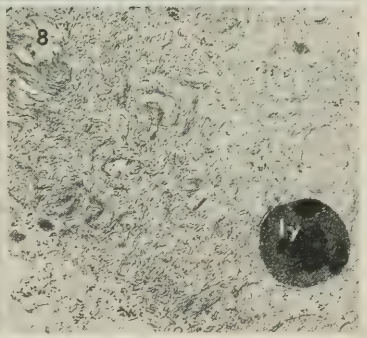


FIGURE 5.—*Two weeks after the exposure. The retina appears to be normal. Arrow indicates the border of the damaged (left) and normal (right) areas.*

FIGURE 6.—*Two weeks after the exposure. The outer segments and the pigment cells show normal structure. Only a few fragments of necrotic substances (arrows) present in the subretinal space. Pigment granules (p) located mainly in the apical portion of the cell. Mitochondria (m) shows an elongated shape. Bruch's membrane (BrM) and choroidal tissue are normal.*

FIGURE 7.—*Vessel preparation of the retina of 2 weeks' damage shows localized small clusters of obliterated capillaries (arrow). The adjacent vessels are normal.*

FIGURE 8.—*Four weeks after the exposure. The cytoplasm of the pigment cell shows the normal appearance. Large lysosome particles (ly) are commonly found.*

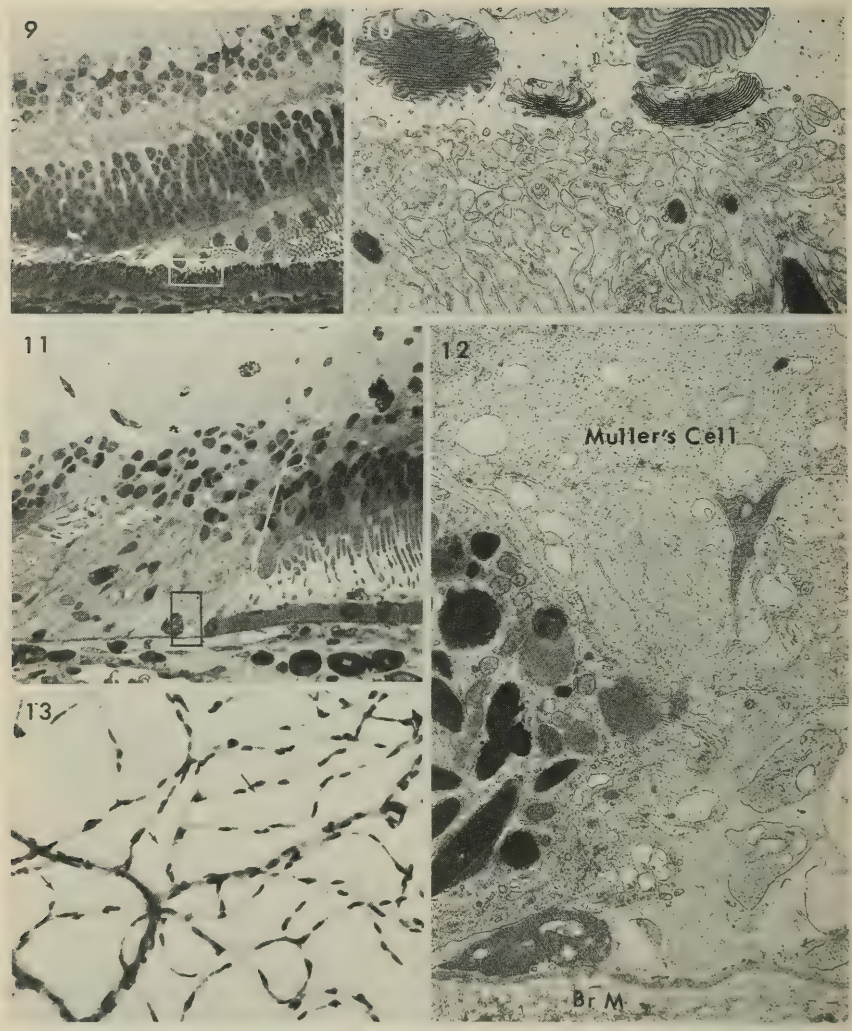


FIGURE 9.—*Two months after the exposure. The pigment cell and the retinal cells have been repaired completely, but the photoreceptor elements are still very small in this area.*

FIGURE 10.—*Electron micrograph of the portion indicated in figure 9. Photoreceptor lamellar membranes are forming in the vicinity of proliferated microvilli of the pigmented cells.*

FIGURE 11.—*Severely damaged focus, 4 months after the exposure. The damaged area has become a sharply demarked scar. Scarred area lacks pigment epithelium.*

FIGURE 12.—*Higher magnification of the portion of figure 11. Muller's cells of the retina adhere to Bruch's membrane (BrM). A portion of a damaged pigmented cell is seen also.*

FIGURE 13.—*Vessel preparation of the retina in which multiple burns were given 4 months previously. The general pattern is normal. Only a few acellular strands (arrows) are seen in the vessel preparation.*

rapidly disappeared and was replaced by normal cells in a short period of time. Even with multiple burns the retina was not left with morphological defect in the exposed area. This finding might confirm the fact that the application of the ruby laser caused little field defect clinically. Since the mitotic activity was not demonstrated in the retina in this experiment, the regeneration of the tissue may have taken place by the rearrangement of adjacent normal cells rather than the formation of new retinal cells. The normal pigment cells might be the first to move into the damaged area. Similar reparative capacity of the pigment cells was described previously. (*4*)

In spite of the prompt repair of the retinal tissue proper, the damaged blood vessels appeared to lack regenerative capacity and were retained in the burned area as clusters of fibrous strands. Since the direct damage on the blood vessels was not demonstrated in the early stage, the vessel degeneration appeared to occur as the secondary process to the degeneration of the retinal tissue. The general vascular pattern of these normal monkey retinas was not altered by the discrete damages of the capillaries. However, the effect of this treatment on pathological retinas with vascular disorder might be different and some hemodynamic alteration in the retinal vessels might occur.

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CHAPTER 55

Fluorescence Microscopic, Autoradiographic, and Histochemical Studies on Human Diabetic and Nondiabetic Eyes: An Abbreviated Report

HANS-WALTHER LARSEN, M.D.
A. U. WERNER

This investigation, comprising at present 17 diabetic and 14 nondiabetic eyes, was carried out in the following ways:

(1) Immunofluorescence techniques employing fluorescein-isothiocyanate (FITC) conjugated insulin—including insulin preincubation assays—and FITC-tagged globulin isolated from diabetic serum.

(2) Autoradiographic examination with iodine-125-labeled insulin—including insulin preincubation assays.

(3) Various histochemical procedures including PAS staining (silver impregnation of reticulin fibers, orcein staining for detection of elastic fibers, demonstration of acid mucopolysaccharides through alcian blue staining, and acridine orange fluorescence examination for determination of nucleic acids—not illustrated in this paper). The results are shown in figures 1–19.

CONCLUSIONS

In diabetic eyes

(1) Fluorescein-isothicyanate conjugated insulin exhibited characteristic binding phenomena to endothelial lining and basement membranes.

(2) Marked silver grain accumulation occurred to the same structures after application of iodine-125-labeled insulin, and

(3) PAS-positivity was more pronounced as compared to nondiabetic eyes.

The binding capacities of FITC insulin varied from structure to structure, and was most pronounced in the ciliary body, the iris, the retina and the choroid.

From the Steno Memorial Hospital, Gentofte, Denmark, and the Ophthalmopathologic Laboratory, Copenhagen, Denmark.

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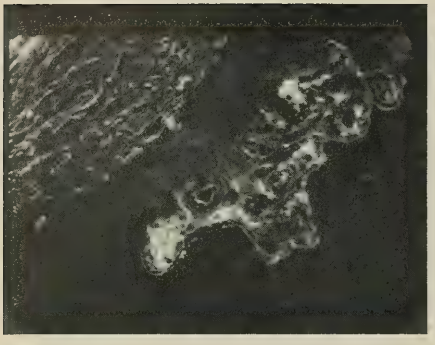

FIGURE 1.—*Ciliary processes from a nondiabetic patient, aged 70 years. Although there is some binding of FITC-insulin to reticular fibers in some of the processes, fluorescence of the vessel walls and basement membranes is absent.*

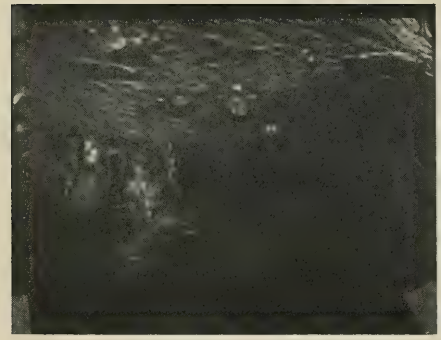

FIGURE 2.— *From the same eye and similar view as in figure 1. The preparation has been preincubated with insulin. Practically no fluorescence is discernible.*

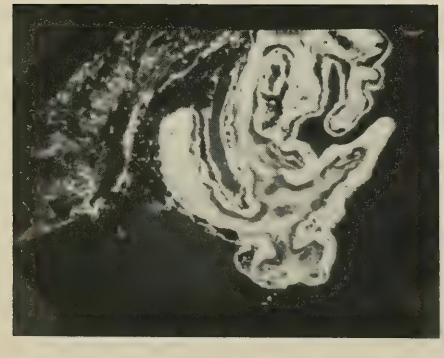

FIGURE 3.—*Ciliary processes from a diabetic patient illustrating fluorescence due to FITC-insulin binding. Observe the heavily stained basement membranes and the marked coloring of the vessel walls in the area.*

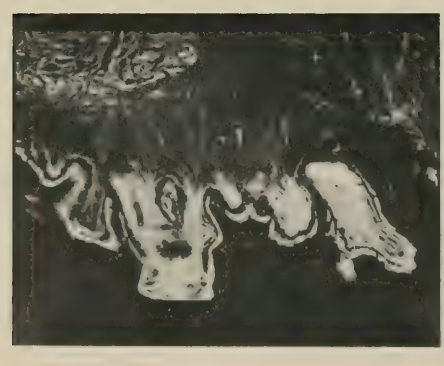

FIGURE 4.—*This section—also from a diabetic—was incubated with diabetic serum. A much higher degree of fluorescence is elicited here than in the ciliary processes of the normal eye shown in figure 1.*

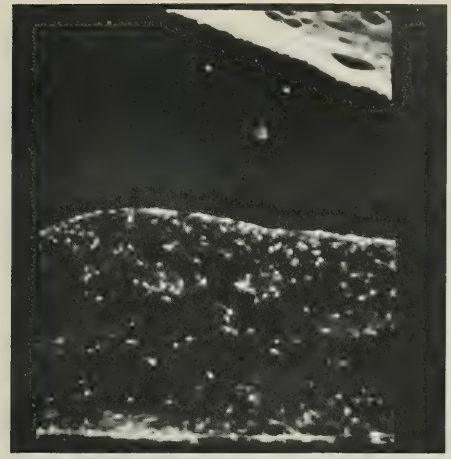

FIGURE 5.—*Part of the iris from a 70-year-old nondiabetic. There is no binding of FITC-conjugated insulin.*

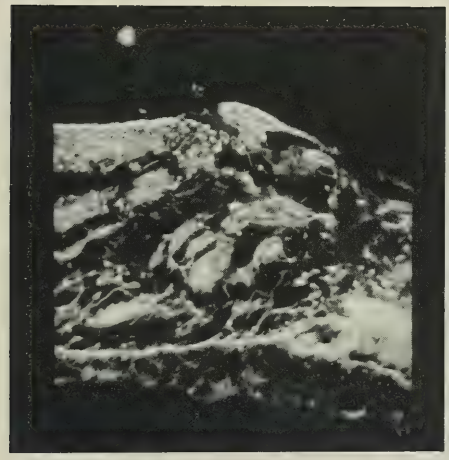

FIGURE 6.—*The iris from a young diabetic aged 30 years with a duration of diabetes of about 19 years. There is pronounced binding of fluorescent FITC-insulin in the vicinity of the vessel walls and especially to the basement membranes. Note the moth-eaten-like alteration of the pigment epithelium—a common finding in longstanding diabetes.*

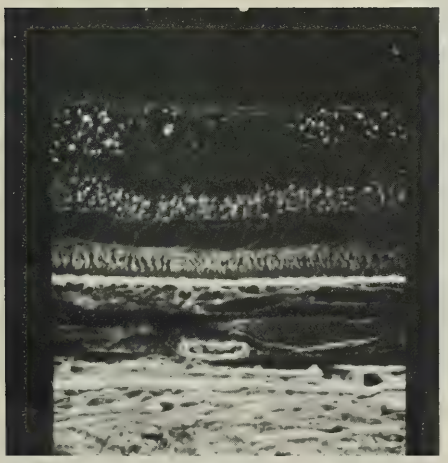

FIGURE 7.—*The retina, choroid and sclera in low magnification from a normal person. The fluorescence of the sclera is partly due to autofluorescence—partly caused by the richness in this structure of reticulin and elastic fibers, which have insulin binding properties.*

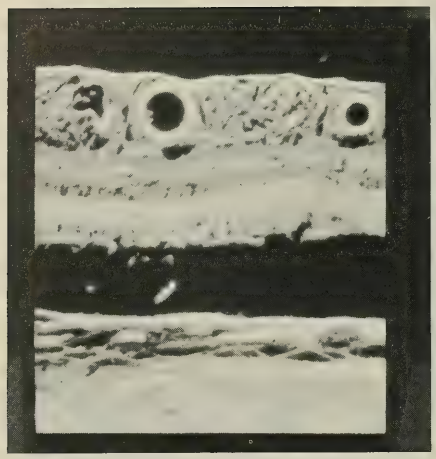

FIGURE 8.—*The retina, choroid and sclera from a diabetic. In the retina two arteries and one vein are brightly fluorescing; in the choroid some of the vessels are fluorescent too.*

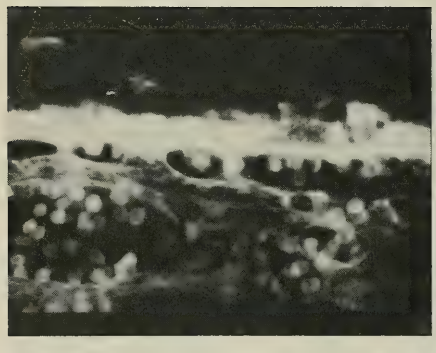

FIGURE 9.—*Close view of the pigment epithelium and the choroidal vessels from a normal person. Bruch's membrane exhibits relatively strong fluorescence—which in fact is an autofluorescence. None of the choroidal vessels are stained by FITC-insulin.*

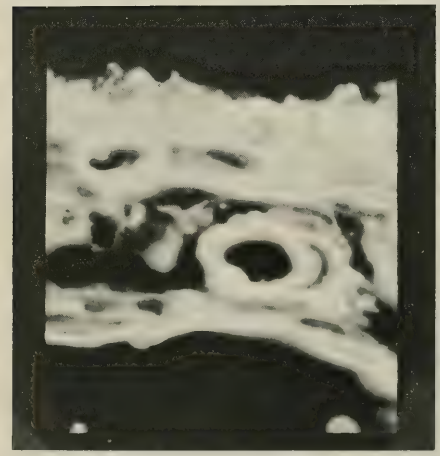

FIGURE 10.—*Close view of the pigment epithelium and the choroidal vessels from a diabetic with longstanding diabetes. The choroidal vessels and Bruch's membrane show heavy FITC-insulin staining capacity.*

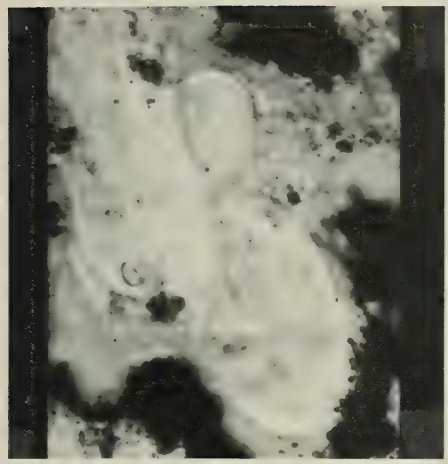

FIGURE 11.—*Ciliary process in high-power view from a nondiabetic person showing the effect of simultaneously PAS-staining and autoradiographic exposure of the section to iodine-125-labeled insulin. There are background silver grains—but no binding to vessels or basement membranes.*

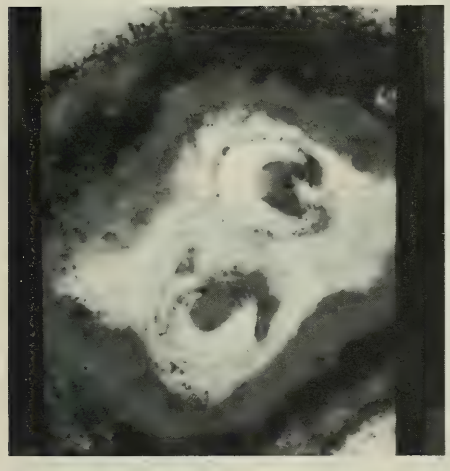

FIGURE 12.—*Ciliary process in close view from a diabetic showing the effect of simultaneously PAS-staining and autoradiographic exposure of the section to iodine-125-labeled insulin. Note the accumulation of silver grains to endothelial lining and basement membranes of the vessels. Note the difference in intensity of PAS-positivity in comparison to the nondiabetic section in figure 11.*

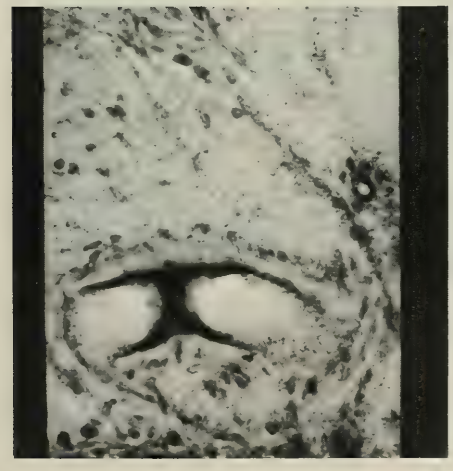

FIGURE 13.—*High-power magnification of the iris from a diabetic. The section is treated in the same way as the section in figure 12. There is a heavy deposition of silver grains over the vessel wall.*

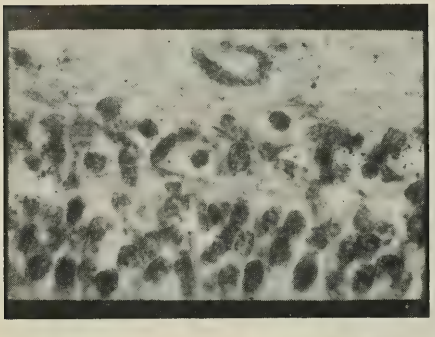

FIGURE 14.—*Close view of a small retinal vessel in a nondiabetic. After autoradiographic exposure to labeled insulin no binding is visible over the vessel wall.*

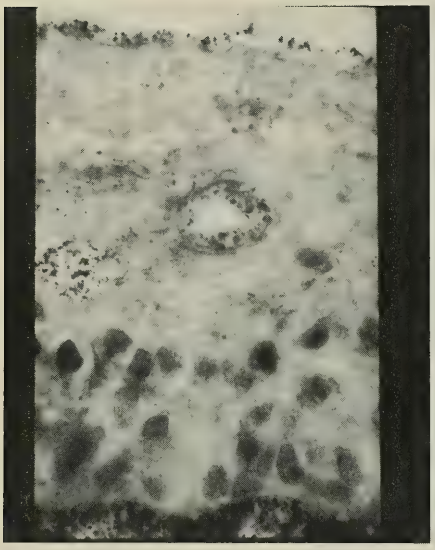

FIGURE 15.—*Retinal vessel of approximately the same caliber in a diabetic exhibiting isotope-labeled insulin binding over the basement membrane structures.*

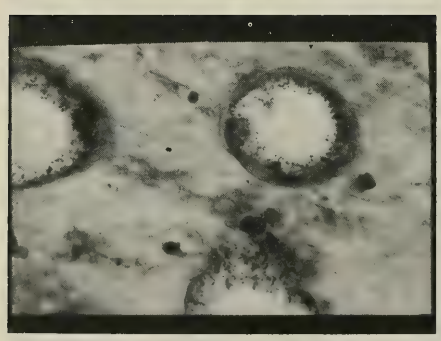

FIGURE 16.—*From a case of proliferative diabetic retinopathy. Insulin-iodine-125-binding over the newformed vessels.*

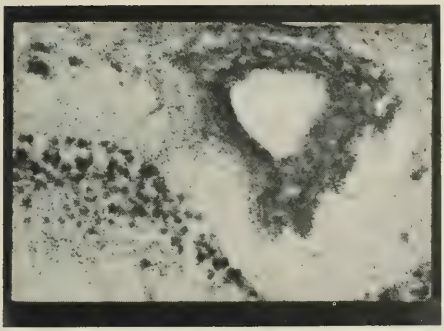

FIGURE 17.—*Binding of the isotope-labeled insulin to a minor retinal vessel in a diabetic.*

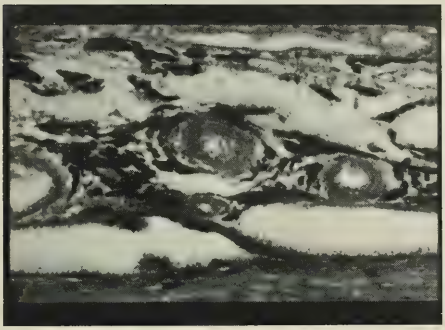

FIGURE 18.—*Simultaneously applied PAS-staining and autoradiographic exposure of the choroid from a diabetic to labeled insulin demonstrating pronounced PAS-positivity of the hyalinized vessels and accumulation of silver grains over the vessels.*

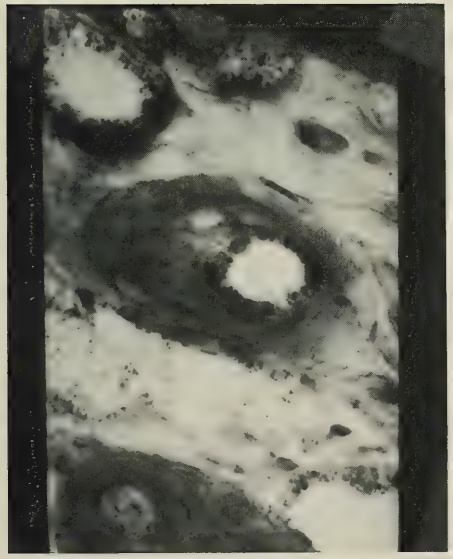

FIGURE 19.—*High-power magnification of choroidal vessels in a diabetic. The section exhibits silver grains corresponding to labeled insulin binding and heavy PAS-positivity.*

The binding has a specific as well as a nonspecific character. The specific reaction was demonstrated by the diminution of binding capacity after blocking the sites with unlabeled insulin.

The nonspecific reaction was preferentially found in the cornea, the sclera and the lens, probably involving disulphide and sulfhydryl linkages, and in pathologically hyalinized tissue and structures especially rich in glycoprotein matters as in melanoma, but to a much lesser degree than seen in diabetic eyes.

The study which has been extended to other structures by A. U. Werner, Steno Memorial Hospital, including skin, gingiva, connective tissue, muscles, etc., shows the same binding capacity in these tissues in diabetics.

The demonstrated immunulogical reactions may be of importance in the metabolism and nutrition of various structures, and therefore may be a co-factor in the development of diabetic retinopathy.

A more detailed report on the subject will appear in Acta Ophthalmologica.

CHAPTER 56

ERG in Juvenile Diabetics: A Prognostic Study

SVEND ERIK SIMONSEN, M.D.

The classical ERG has, to date, not proven to be of much value in terms of clinical application to the problem of diabetic retinopathy.

Investigations made by Francois *et al.* (*1*), Straub (*2*), and Karpe *et al.* (*3*) have shown that the classical ERG does not exhibit significant changes until very advanced retinopathy is present. The exceptions here are a few cases with only slight retinopathy, shown by Karpe *et al.* (*3*) to have supernormal ERG, probably because of venous stasis.

Yonemura *et al.* (*4*) showed by means of another electroretinographic technique that the so-called oscillatory potential, a relative recently discovered component of ERG, was selectively reduced even in very early cases of diabetic retinopathy. This has since been confirmed by Sugita *et al.* (*5*), Simonsen (*6*, *7*), Kojima *et al.* (*8*), Tassy (*9*), Jacobson *et al.* (*10*), and Nakajima *et al.* (*11*).

Henkes' (*12*) periodical integration of selectively amplified flicker ERG also seems to show electrophysiological disturbance in early cases of diabetic retinopathy.

The result of these latter investigations seems to increase the possibility of obtaining valuable clinical information by using a more detailed ERG technique.

The purpose of the present investigation was to compare the ERG from a group of diabetics with normal subjects, especially with reference to the oscillatory potential and to investigate to what extent the ERG is helpful in prognosis.

MATERIAL AND METHODS

The investigation was carried out at Steno Memorial Hospital, a special hospital for diabetics (chief, Dr. J. E. Poulsen). ERG was recorded in 275 eyes from 141 diabetics ranging in age from 17 to 50 years. All diabetics were of the juvenile type. A thorough ophthalmoscopy combined with retinophotography was carried out.

From Steno Memorial Hospital, Gentofte, Denmark.
Present address, Department of Ophthalmology, University Hospital, Tagensvej, Copenhagen.

At first examination, only eight out of the 275 diabetic eyes had a corrected visual acuity $\geq 6/12$, and no eyes were below 6/60.

The normal material were 50 eyes from 26 nondiabetics with normal visual acuity, ophthalmoscopic appearance, and color vision as tested by the Ishihara tables.

Both the diabetic and the normal material was limited to subjects with a refraction within ± 3 diopters.

After 20 minutes dark adaptation, the ERG was obtained simultaneously from both eyes using Karpe's contact lenses. Recording was done by photography of five superimposed responses from the screen of a double beam oscilloscope. The frequency range of the system was 2 to 500 cycles per second or 20 to 500 cycles per second. The photic stimulator was an electronic flash of a high and variable intensity. Flash intervals were set at 15 seconds. (More methodological details: Simonsen, 1968.(7))

RESULTS

Figure 1 shows ERG's as response to the strongest flash. At the top, typical normal ERG from a nondiabetic; the pair of ERG's represent the right eye at the top and the left eye at the bottom. In the second

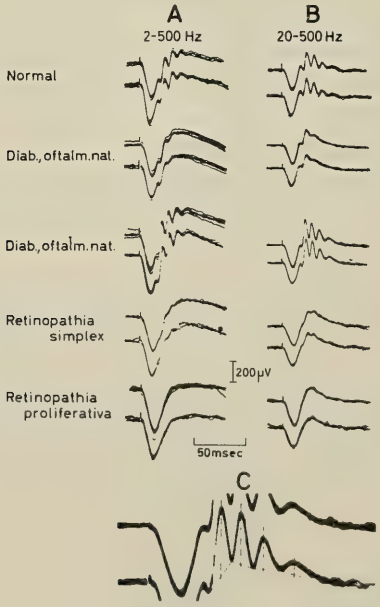

FIGURE 1

row, the ERG's from a patient with diabetes for 5 years, no retinopathy, but nevertheless reduced oscillations. In the fourth row, the ERG's from a patient with diabetes for 10 years and simple retinopathy (scattered microaneurysms and small hemorrhages) show the oscillations are greatly reduced. In the fifth row, the ERG's from a case of proliferative retinopathy with oscillations completely extinguished. In the third row are, finally, the ERG's from a patient 33 years old with 17 years of diabetes but without any visible retinopathy. The oscillations are here hypernormal. Hypernormal oscillations have not been described before. They seem to be a characteristic feature of eyes from diabetics who have got along for an unusually long time without developing even the slightest retinopathy (see fig. 3). Series B is identical with series A, only recorded in another frequency range, which reduces the "classical" waves (the negative a-wave and the positive b-wave), but not the high frequency oscillatory potential, which is superimposed on the ascending slope of the positive b-wave. Each ERG in figure 1 consists of five superimposed responses. In an attempt to obtain a measure of the size of the oscillations, the amplitudes were added as shown under C (Simonsen, 1965 (*6*)). Since the author interprets the oscillations as approximately sinusoidal waves superimposed on a smooth curve (see also Jacobson *et al.* (*10*)), the amplitudes were measured as shown in C from the connection lines to the peaks. The sum of these amplitudes give an expression of the deviation from the imaginary smooth curve. (A similar method has since been used by Usami (*13*) and Algvere (*14*).)

In figure 2, the added amplitudes of oscillations from the single normal eyes have been expressed as a function of age in years. The individual deviations are small, and no systematic change is seen because of age in this group between 17 and 50 years. The mean value and $\pm 2x$ the standard deviation is shown. Sixteen eyes from nine subjects were re-examined 1 to 2 years later and only show very small changes.

In figure 3 the added amplitudes from the single diabetic eyes are expressed as a function of the number of years after the age of 14 that the patient had suffered from diabetes. The total number of years with diabetes was not used in order to compensate for the fact that diabetic retinopathy has not been definitely demonstrated prior to puberty, but generally occurs 6 to 10 years later. This is approximately the same number of years that elapse, on the average, before visible retinopathy manifests itself in juvenile diabetics whose diabetes has set in after puberty.

The open circles represent diabetic eyes without visible retinopathy; the oblique strokes represent eyes with simple retinopathy; and the

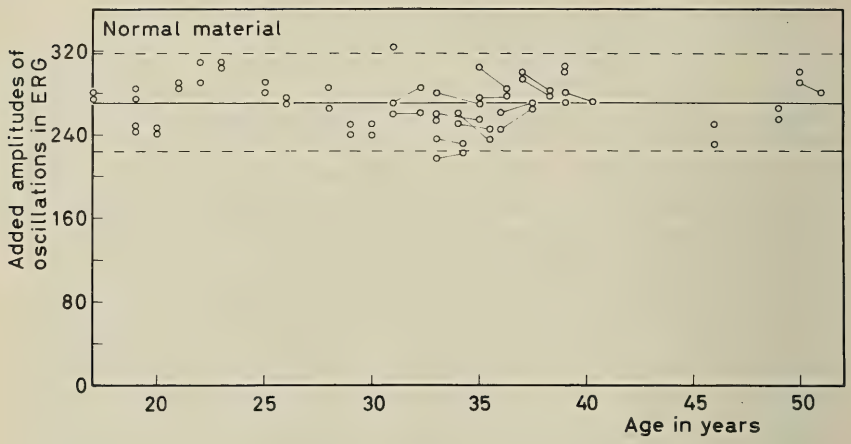

FIGURE 2

filled circles, eyes with proliferative retinopathy. The mean value and ±2x the standard deviation for the normal material are shown.

Cases with proliferative retinopathy show extinguished or significantly reduced oscillations, even though a- and b-waves usually are within the normal range. Proliferative cases with only small peripheral, eventually burned out proliferations usually show bigger oscil-

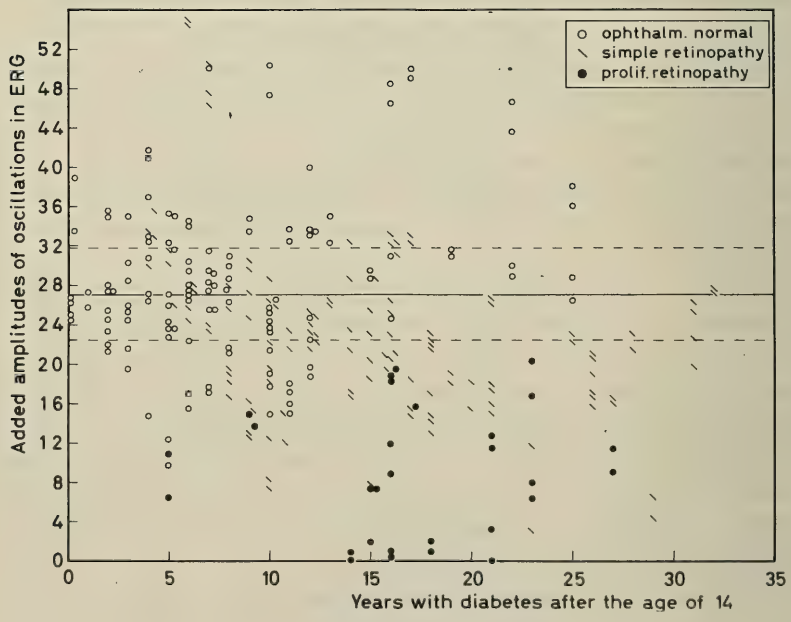

FIGURE 3

lations than proliferative cases with prepapillary proliferations whose prognosis is usually worse.

Cases with simple retinopathy are not further differentiated here for the purpose of simplicity. Cases above the level "32" show only one or two microaneurysms, and usually the more hemorrhages and exudates there are, the more reduced are the oscillations.

A matter of particular interest is that a large number of the open circles, which represent diabetic eyes without visible retinopathy, differ significantly from the normal eyes. This means that electrophysiological disturbance often precedes ophthalmoscopically demonstrable changes. The blood sugar level at the time of the investigation was not found to influence the size of the oscillations. Hypernormal oscillations occurred predominantly in cases of longstanding diabetes without retinopathy.

Sixty of these eyes from 30 diabetics were reexamined by ERG 1 to 2 years later, and the result is shown in the diagram, figure 4.

In figure 4 most eyes show reduction of the oscillations as a function of time. In some cases the change is not greater than what could be seen in the normal material (fig. 2), but in many cases the reduction seems to be significant.

Figures 5 and 6 show examples of simultaneous change in ERG and retinal picture. The patient represented by figure 5 was a 37-year-old

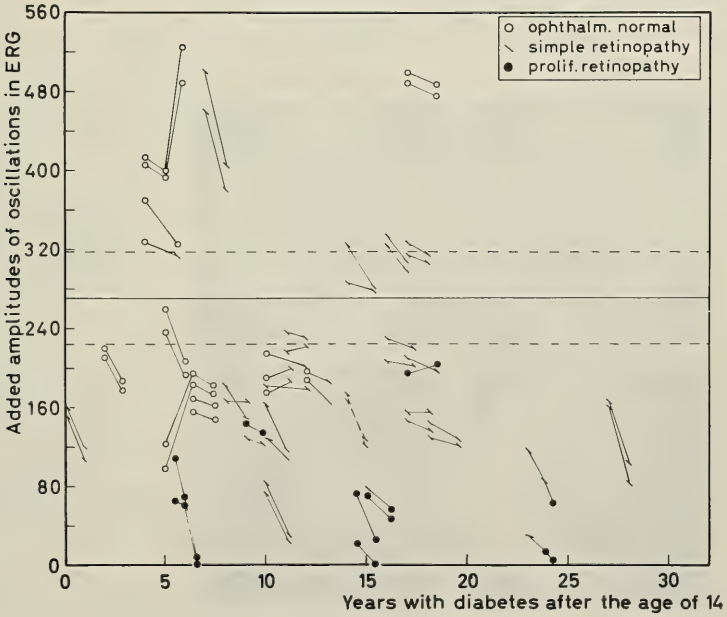

FIGURE 4

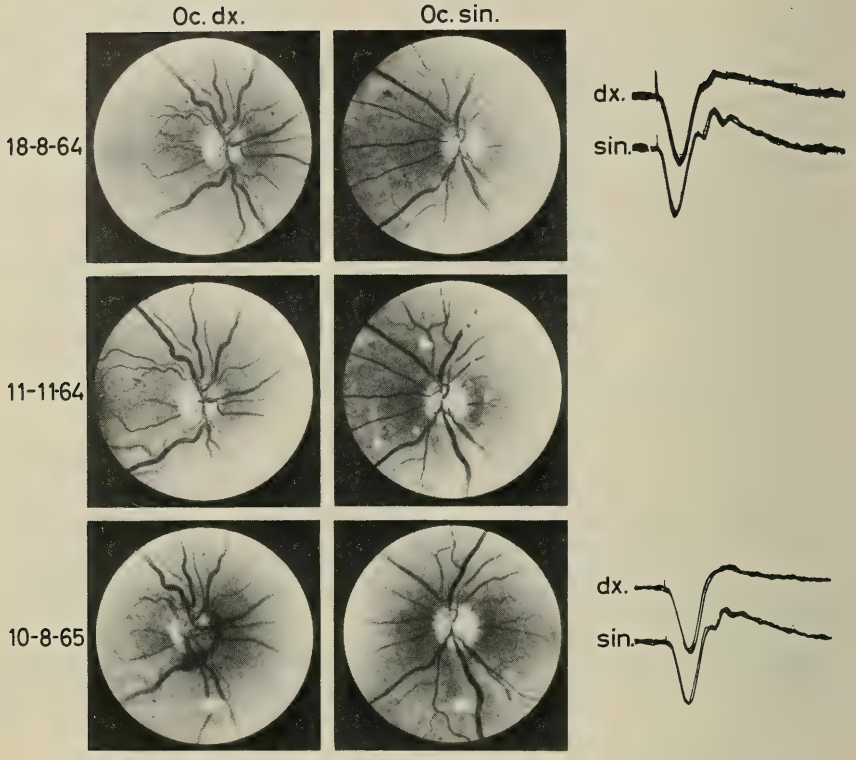

FIGURE 5

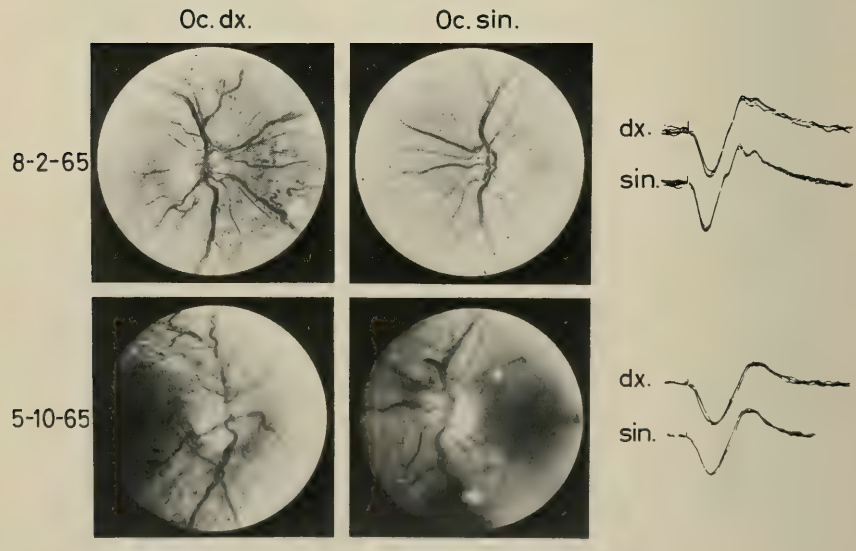

FIGURE 6

woman with diabetes since the age of 12. At the first examination there was a moderate, simple retinopathy in both eyes and no eye complaints. Nevertheless, the oscillatory potential was greatly reduced in the left and almost extinguished in the right eye. Three months later, the first little proliferative vessel sprout had appeared on the temporal part of the right papilla; 9 months later again this had developed into a great prepapillary tuft, and the first fine new-formed vessels had appeared at the left papilla. Reexamination by ERG showed further reduction of the oscillatory potential.

The patient represented by figure 6 was a 19-year-old female with diabetes since the age of 7. At the first examination there was a proliferative retinopathy in both eyes, and the oscillatory potential was greatly reduced. Eight months later the proliferative lesions were much more serious, and preretinal and vitreous hemorrhage had appeared in the left eye. The oscillatory potential was now completely extinguished.

For the moment a followup study of the diabetics is being made, and the preliminary result is demonstrated in the diagram figure 7. One hundred and eight eyes from 55 of the diabetics were reexamined by ophthalmoscopy combined with retinophotography 1½ to 4½ years after the initial ERG examination, and the retina photos from the first and the second examination were thoroughly compared. Statistical

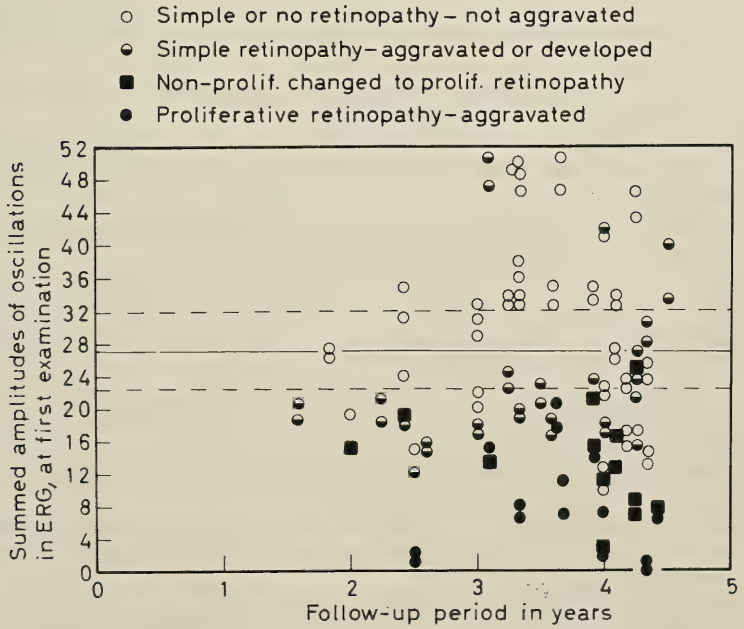

FIGURE 7

evaluation of this followup study has not been made yet, but the diagram leaves no doubt that ERG in this method can be used for prognostic evaluation of diabetic retinopathy. Most diabetic eyes with normal or hypernormal oscillatory potential do not show aggravation of the retinal changes in the followup period, while most eyes with reduced oscillatory potential do show aggravation, often from nonproliferative to proliferative state.

CONCLUSIONS

(1) ERG may, in this method, show significant changes, even before visible retinopathy is present.

(2) Reexamination by ERG often shows a distinct change in the oscillatory potential within 1 to 2 years.

(3) Diabetics without visible retinopathy in spite of longstanding diabetes very often show hypernormal oscillatory potential.

(4) Recording of the oscillatory potential in ERG can be used for prognostic evaluation of diabetic retinopathy.

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CHAPTER 57

A Comparison of Methods of Treatment for Diabetic Retinopathy

ANDREAS M. KOEHLER
RAYMOND N. KJELLBERG, M.D.
J. WALLACE McMEEL, M.D.

INTRODUCTION

An unusual opportunity for objective comparisons between several methods of treatment for diabetic retinopathy is provided by the data on individual patients and eyes supplied by some of the contributors to the U.S. Public Health Service *Symposium on the Treatment of Diabetic Retinopathy*. We have attempted to make comparisons based on the visual acuity data supplied.

DESCRIPTION OF THE DATA

A standardized format for the reporting of diabetic retinopathy data, known as the O'Hare data sheet,[1] had been established prior to the symposium, and invited contributors were urged to supply data on their own cases in this format. Data sheets from 12 groups of contributors were available to us, but one group had to be excluded because the data were incomplete. The 11 groups used for analysis are given in table I. Some groups have reported on more than one method of treatment, but the number of cases and the length of followup in the second or third subgroup has been too small to warrant analysis at this time; hence only the cases treated by the principal method have been included. When retinal photocoagulation has been used, only the treated eyes were included in our analysis. Finally, it was essential to know pretreatment visual acuity for each eye, together with enough information to specify the number of months during which vision was sustained and the number of months that the condition of the eye was followed. The reasons for which eyes were excluded from analysis can then be summarized as—

(*a*) Not treated.
(*b*) Treated by method other than principal method.

[1] Editors' note: These data sheets appear as Appendices A through N.

Cyclotron Laboratory, Harvard University, Cambridge, Mass.

TABLE I.—*Papers analyzed and principal results*

Reference No.	1st author	Technique	Average pretreatment visual acuity [1]	At 30 months after treatment Eyes sustained / Eyes followed ×100%	Confidence limits [2]
1	Dobree	Photocoagulation	0.63	[3]	
2	Field	Stalk section	0.44	84	73–91
3	Hardy	Transsphenoidal	0.34	[3]	
4	Harris	Photocoagulation	0.45	[3]	
5	Kjellberg	Proton beam	0.29	49	38–61
6	Mortimer	Photocoagulation	0.31	64	30–90
7	Okun	do	0.36	88	79–95
8	Pearson	Y^{90} implants	0.24	44	27–64
9	Roth	Photocoagulation	0.43	[3]	
10	do	Cryohypophysectomy.	0.30	71	41–92
11	Wetzig	Photocoagulation	0.36	74	61–84

[1] See text for explanation of the decimal notation.
[2] See text for the basis of calculated confidence limits.
[3] Less than 10 followed.

(*c*) No pretreatment visual acuity given.
(*d*) Duration of sustained vision not accessible.
(*e*) Duration of followup not accessible.

Some inconsistencies in the reporting of results became obvious through study of the data sheets and suggest that certain standards be agreed to for future use. Most important would be to agree on a definition of "vision retained" or "vision sustained." From the data, it appears that one author considers vision retained so long as the eye is capable of counting fingers, regardless of the visual status before treatment, while another author apparently accepts no reduction in visual acuity whatsoever. The practice of most authors seems to fall between these extremes, but few of them have been explicit. We have used the data as reported, but emphasize that some bias is present when comparisons are made.

Another source of this bias may be introduced by the type of evidence which is accepted to establish that vision has been sustained. It is our feeling that a test with an eye chart administered by a professional should be required and that the "duration of followup" should be the interval from treatment to the last such test recorded. Also there appear to be a few careless arithmetical errors scattered here and there through the data sheets.

PRETREATMENT VISUAL ACUITY

Acuity ratios commonly recorded were converted to decimals: for instance, 20/20=1.0, 6/18=0.33. Values of 0.03, 0.02, and 0.01 were assigned to CF, HM, and LP so that they could be included in calcula-

tions. For each group of treated eyes, the distribution of pretreatment visual acuity was then compiled and converted to a cumulative percentage distribution such as shown in figures 1(a) through 11(a). This form of distribution was chosen because the sizes of intervals on the standard acuity chart are uneven, and also because readings from unusual standard charts had to be accommodated. (See references 1 and 6, for instance.) From these distribution graphs, one can read the percentage of eyes within a group having visual acuity less than or equal to any value chosen on the visual acuity scale. For instance, referring to figure 1(a), in this group, 29 percent of treated eyes had acuity less than or equal to 0.33, while figure 2(a) shows 43 percent less than or equal to 0.33.

Differences among the distribution curves are immediately obvious and are assumed to be the consequence of different selection criteria used in accepting or refusing cases for treatment. For example, the groups treated by pituitary ablation usually show a fairly large fraction of eyes with quite bad acuity (as compared to the typical photocoagulation group) since the patient's worst eye is automatically treated along with the better, whereas this treatment may be omitted when photocoagulation is employed. In order to keep track of these differences in a simple way, the average pretreatment visual acuity was calculated for each group. (See table I.)

LIKELIHOOD OF VISUAL RETENTION

Within each group the number of eyes with vision sustained 3 months or more after treatment was obtained. Similarly the number of eyes that were followed 3 months or more was obtained. The ratio of these two numbers is our best estimate, based on the data supplied, of the average likelihood that an eye acceptable for this method of treatment will have vision sustained at 3 months after treatment. The observed value is related to the "correct" value, which would be obtained with an infinitely large number of such cases through the binomial distribution law. The 95-percent-confidence limits for the deviation of the "correct" value from the observed have been obtained on this basis (*12*).

Similar computations have been made at 6, 10, 20, and 30 months after treatment until the number of eyes followed dwindled to less than 10. The results are shown in figures 1(b) through 11(b).

Several of the graphs show an initial drop within the first 6 months or so, followed by a "plateau" of lesser slope. We felt that the level of this plateau, indicative of the long-term likelihood of visual retention, was the most significant characteristic and warranted further study. We have taken the value calculated for 30 months to be indicative of the level of the plateau. (See table I.)

FIGURE CAPTIONS

Figures 1 through 11

Analysis of pretreatment visual acuities and of retention of vision after treatment in 11 groups of eyes treated for diabetic retinopathy: The figure numbers are keyed to the numbers of the references from which the data were taken. In each figure (a) represents the cumulative distribution of visual acuities before treatment recorded for the group of eyes. For instance figure 1(a) shows that 29 percent of eyes from this group had visual acuity equal to or less than 0.33 (which is given as 6/18 in the data). In each figure (b) shows the ratio of the number of eyes with vision still sustained at a particular length of time divided by the number of eyes that were followed for at least that length of time. This ratio has been expressed as a percentage. The error bars show the 95 percent confidence limits calculated for this ratio (see text).

Figure 12

Visual retention at 30 months *versus* average visual acuity before treatment. The points are identified with the number of the reference from which the data were taken. Squares indicate the results of pituitary ablation; circles, retinal photocoagulation. The error bars represent 95 percent confidence limits. The dotted line represents a possible relationship between the two variables. Note that the data for point 7 are not strictly comparable to some of the others and tend to make it too high (see text).

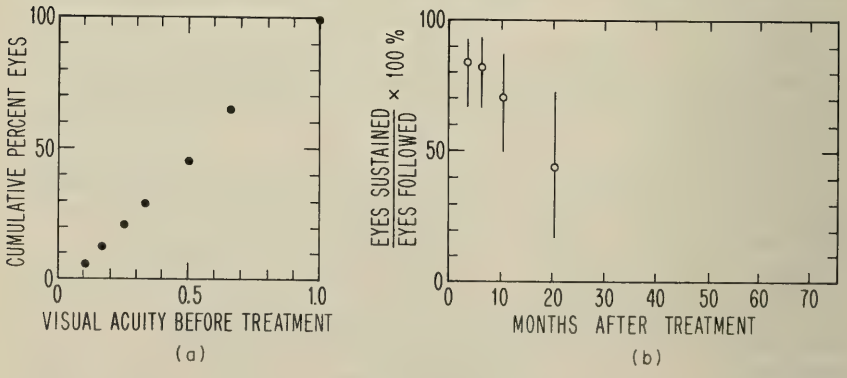

FIGURE 1.—*J. H. Dobree (photocoagulation).*

FIGURE 2.—*R. A. Field and others (pituitary ablation).*

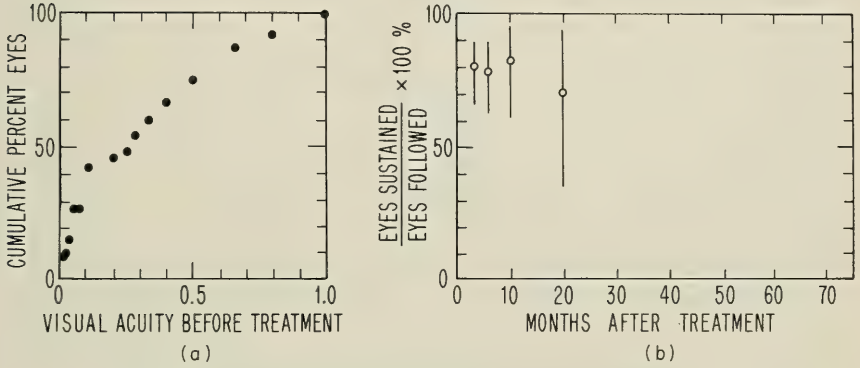

FIGURE 3.—*J. Hardy and others (pituitary ablation).*

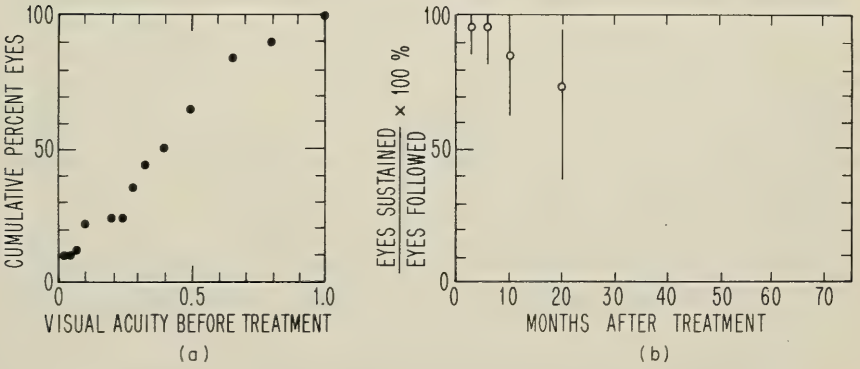

FIGURE 4.—*G. S. Harris (photocoagulation).*

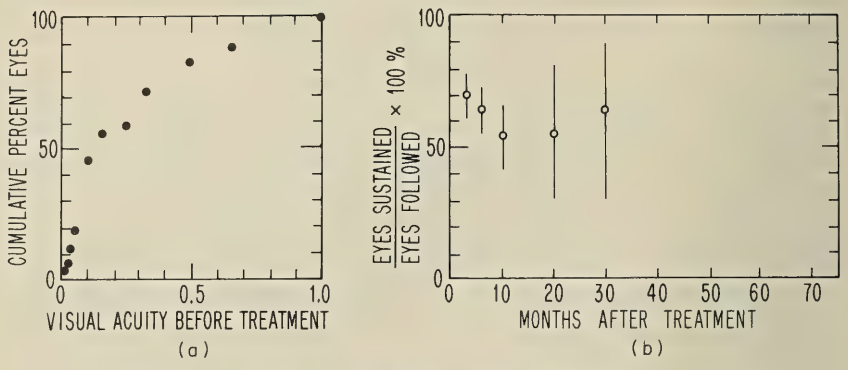

FIGURE 5.—*R. N. Kjellberg and others (pituitary ablation).*

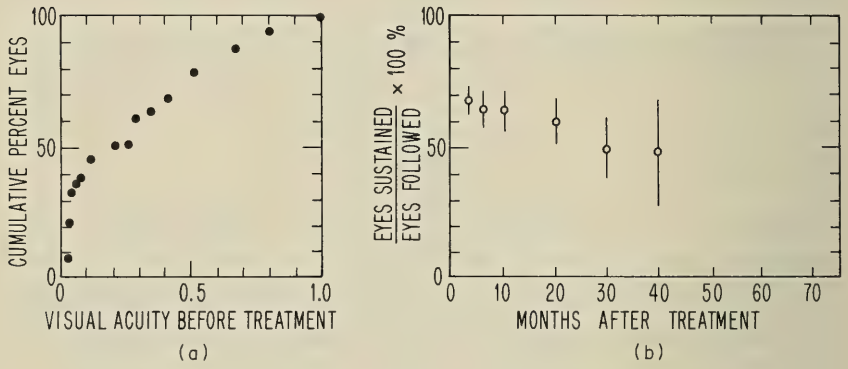

FIGURE 6.—*C. B. Mortimer (photocoagulation).*

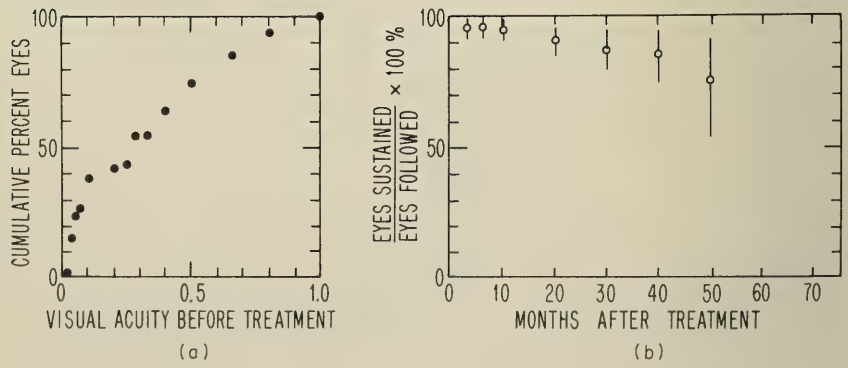

FIGURE 7.—*E. Okun and G. P. Johnston (photocoagulation).*

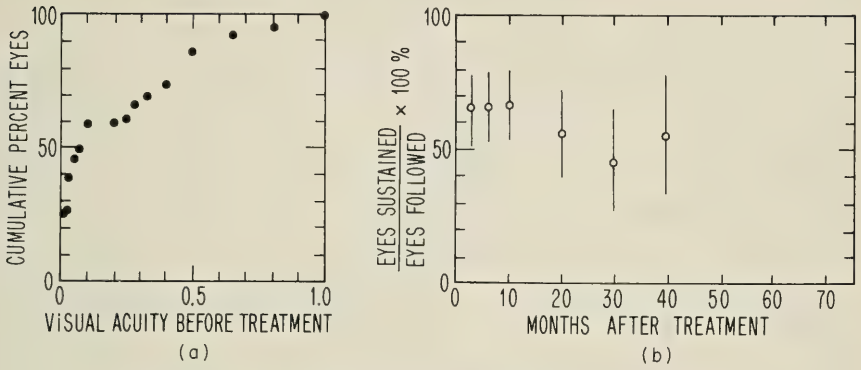

FIGURE 8.—*O. H. Pearson and others (pituitary ablation).*

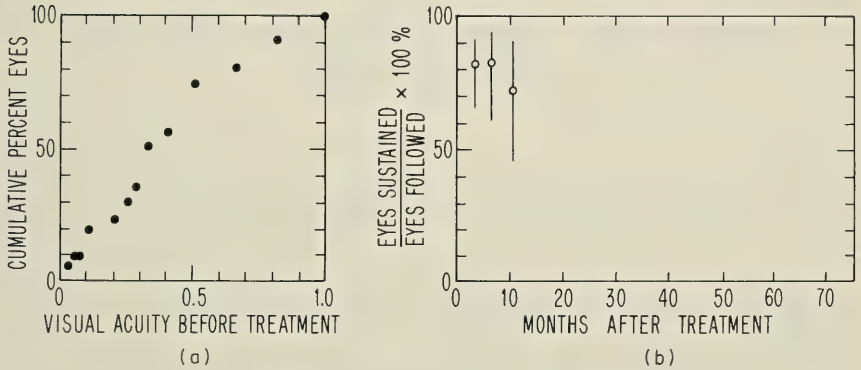

FIGURE 9.—*N. H. Roth and R. W. Rand (photocoagulation).*

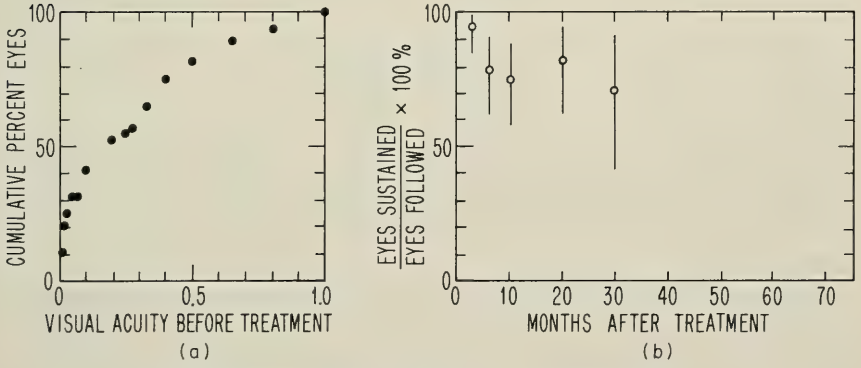

FIGURE 10.—*N. H. Roth and others (pituitary ablation).*

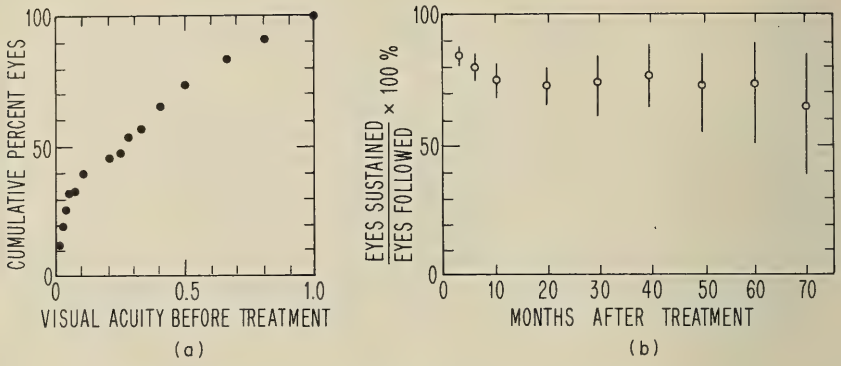

FIGURE 11.—*P. C. Wetzig and C. N. Jepson (photocoagulation).*

LONG-TERM VISUAL RETENTION RELATED TO SELECTION

We have taken the average value of visual acuity before treatment to be a rough indication of the average severity and state of advancement of disease characteristic of each group. Only a statistical association is assumed; any individual case with good acuity may actually have very active disease, and one with poor acuity may in fact be relatively well. On the average, however, it seems reasonable that the more grave the disease state, the poorer the typical visual acuity. More stringent selection criteria, tending to screen out from treatment cases with severe and advanced disease, will therefore result in a higher value of average pretreatment visual acuity.

In figure 12 we have plotted our estimate of the likelihood of vision being sustained 30 months against the average visual acuity before treatment, for each of the groups with adequate data. The dotted line represents a possible relationship between these variables. Only one of the experimental observations is off the line by more than its confidence limit, and that point appears to have a statistical bias because of the particular definition used for visual retention. Four out of the remaining six points fall within one standard deviation of the dotted line.

We have made similar plots for 10 and 20 months after treatment which indicate that a similar relationship between selection and effectiveness of treatment exists. After making allowance for the statistical bias mentioned, the experimental points can be fitted adequately by a straight line.

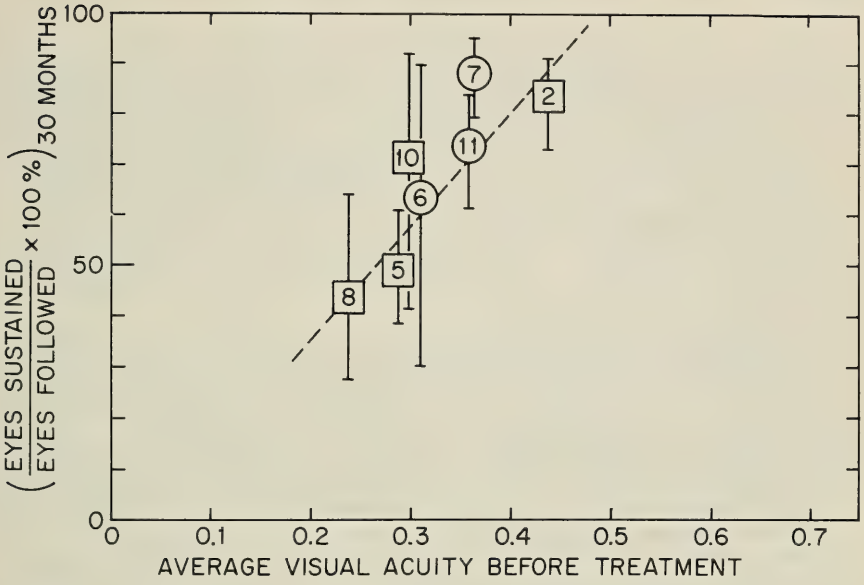

FIGURE 12

COMPARISON OF METHODS

It would be interesting to look for similar correlations using more specific measures of the degree of selection such as the average grade of angiopathy or proliferative retinopathy before treatment. Visual acuity, however, provides a convenient, well-standarized numerical scale with sufficiently fine divisions tending to summarize the effects of these and other parameters.

CONCLUSION

The selection of cases is an important factor determining the likelihood of success of any therapeutic treatment. We have used the average visual acuity before treatment as an indicator of the degree of selection effective in groups of cases of diabetic retinopathy treated by several methods. There appears to be a strong correlation between the degree of selection indicated in this way and the likelihood that vision will be sustained for 1 to 3 years. Assuming this correlation to be real, or at least plausible, the differences in apparent rates of success of the several treatment methods appear to stem from the criteria of selection rather than from differences of inherent effectiveness. We do not argue that pretreatment visual acuity itself is necessarily a prime factor influencing the outcome.

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CHAPTER 58

Proliferative Diabetic Retinopathy: Comparison of Visual Results in Various Treatment Categories

MATTHEW D. DAVIS, M.D.
FRANK L. MYERS, M.D.

One of the major aims of the symposium was to assemble data concerning pituitary ablation and photocoagulation from many centers and, on the basis of this, to provide the practitioner with more clear-cut guidelines than have been available to date for management of patients with diabetic retinopathy. With this end in view, a very abbreviated classification ("O'Hare Classification")[1] was devised and recommended to all participants.

The purpose of the classification was to divide eyes into groups with similar findings so that results of different centers could be compared. This purpose was served reasonably well; but the classification had many defects, some recognized initially and others apparent only after trial. It was realized initially that its retrospective nature was a serious drawback, and the classification was purposely made very coarse in order to allow more uniform application. It was clear that significant deterioration might occur in many individual eyes which would yet be insufficient to move the eye into a more severe group in the classification; and that reliance would, therefore have, to be placed on retention of visual acuity as the chief criterion for "success." Unfortunately, the urgent necessity for formulation of more specific criteria for reporting of visual acuity results was not clearly apparent at the initial meeting of the classification committee. Consequently, the classification did not request tabulation of posttreatment visual acuity at specific intervals (1 year, 2 years, 3 years, etc.) but only at the final visit, thus making it difficult to compare series of patients with differing followup periods. It had been anticipated that the "visual retention index" would make the necessary allowance for this, but this term was not specified clearly enough to insure uniform interpretation by all authors, some of whom defined the numerator of the

From the Department of Surgery (Ophthalmology), University of Wisconsin Medical School, Madison, Wis.

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[1] O'Hare Classification, p. xxi.

term as the number of months with maintenance of pretreatment visual acuity or better, while others apparently chose the number of months during which "useful vision" was preserved. Some authors did not provide their raw data, and in such cases it was not always clear just what constituted a "success" (i.e., visual acuity same or better than pretreatment, vision no more than one line worse than pretreatment, etc.).

In general it did not seem possible to make valid comparisons between groups of eyes for which raw data was not presented. Furthermore, the use in some series of systematic factors (renal function, blood pressure, age, etc.) and/or "documented progression" of the retinopathy as criteria for selection of patients for treatment made comparisons between groups hazardous even when raw data was available. In spite of all these difficulties, we felt that it would be of considerable interest to compile and compare all raw data provided. This analysis, although not completed in time for presentation at the symposium, is set forth below.

The raw data of all participants providing it [1] has been pooled and divided into three groups: pituitary ablation, photocoagulation, and "control." The latter group includes patients receiving no treatment (University of Wisconsin, Dobree), patients in whom an attempt was made to improve diabetic control (Hammersmith Hospital) and fellow eyes of patients undergoing photocoagulation in one eye (Dobree, Okun). Only eyes followed for at least 1 year have been included, and the criterion of success chosen was maintenance of pretreatment or better visual acuity at the most recent followup visit. All available data have been compiled in table I. As indicated in the table, several categories of the O'Hare Classification have been combined. The decision to combine category $N_1F_0H_1$ with $N_2F_0H_1$, category $N_1F_1H_0$ with $N_2F_1H_0$ and category $N_1F_1H_1$ with $N_2F_1H_1$ was reached after study of our own data (table I, ch. 7) showed that the results in categories to be combined were essentially the same and that combination would yield groups large enough for meaningful statistical analysis. The same conditions prevailed in regard to the $N_1F_2H_0$ and $N_1F_2H_1$ categories and the $N_2F_2H_0$ and $N_2F_2H_1$ categories, but the chief reason for combining them was to allow inclusion of the data of McMeel and coworkers (table 8, ch. 26), whose raw data was not available. Their data specifies patients rather than eyes; but since in 80 percent of their patients, the fellow eye had visual acquity of 20/200 or less and the results recorded apply almost exclusively to the "good" eye, probably no great error results from treating their data as eyes.

[1] Since only 2 months were available to the participants for the prodigious task of compiling even the limited data required by the O'Hare Classification, it is not surprising that only a minority of participants provided raw data suitable for analysis.

TABLE I.—*Proliferative diabetic retinopathy: Eyes with visual acuity same or better than pretreatment after 1 year or more* [1]

First author	Myers	Dobree	Okun	Kohner	Kjellberg	McMeel	Hardy	Pearson	Roth	Mortimer	Harris	Larsen	Dobree	Okun	Wetzig
Treatment	None	None	None	Improved control of diabetes	Bragg peak proton beam	Stalk section	Trans sphe-noidal surgical hypoX	Several methods	Trans sphe-noidal cryo hypoX	Xenon photo-coagu-lation	Xenon photo-coagu-lation	Xenon photo-coagu-lation	Xenon photo-coagu-lation	Xenon photo-coagu-lation	Xenon photo-coagu-lation
CLASSIFICATION															
$N_1F_0H_0$	17/47	8/17	18/24	11/23	5/9	----------	4/6	6/10	3/3	1/2	4/4	6/8	3/5	8/20	9/9
$N_2F_0H_0$	6/24	2/3	3/6	4/4	0/4	----------	2/2	0	0	0	0	1/3	1/4	17/34	1/4
$N_1N_2F_0H_1$	4/20	0/1	6/12	0	0/2	----------	0	4/11	1/1	5/13	1/2	1/1	0/2	27/50	13/17
$N_1N_2F_1H_0$	6/9	3/13	2/6	2/8	7/14	----------	1/2	0	2/2	0	3/6	2/3	4/6	10/16	4/5
$N_1N_2F_1H_1$	7/26	0/4	1/9	0	8/24	----------	0	8/11	3/5	6/12	2/3	0	1/1	13/37	17/32
$N_1F_2H_0H_1$	7/19	4/7	0	1/3	10/21	4/6	0	13/23	3/3	1/2	1/2	0	1/4	0	4/6
$N_2F_2H_0H_1$	5/26	0/1	6/17	0	13/33	40/59	4/6	5/6	5/6	0/4	2/3	2/4	0/4	9/21	31/61

[1] The numerator of each fraction is the number of eyes maintaining visual acuity the same as or better than pretreatment at their last observation. The denominator is the total number of eyes followed 1 year or more.

In table II, all eyes receiving comparable forms of treatment have been lumped together; and the possible significance of differing results analyzed, using the Chi square test.[1] It must be emphasized that the statistically significant differences found between control and treated groups are not necessarily due to treatment, but may instead result from differences in the selection of patients. For example, in the University of Wisconsin series, all patients examined have been considered, including some that probably would not be selected by any of the other investigators for their treatment groups because the degree of retinopathy was either too severe or too mild. Most eyes from the University of Wisconsin series with retinopathy too mild for selection into the treatment groups will presumably be found in the $N_1F_0H_0$ category, which also contains, from the "control" series of Dobree and Okun, the less severely involved fellow eyes of patients whose more severely involved eye was treated with photocoagulation. Inclusion of these eyes in the control series would improve results and tend to obscure any difference between control and treated groups due to improvement from treatment. It is therefore of considerable interest that eyes in the $N_1F_0H_0$ group that were treated either by pituitary ablation or photocoagulation did somewhat better than the controls, the difference barely reaching a significant level when all eyes treated (by either method) were pooled. Furthermore, when the untreated eyes of Dobree and Okun were eliminated from the "no treatment" group, the difference between "no treatment" and each of the treatment groups became statistically significant.

In patients with more severe neovascularization but still in an early stage of proliferative retinopathy without fibrous proliferation extending into the vitreous cavity or vitreous hemorrhage ($N_2F_0H_0$), results in the control group were worse (than $N_1F_0H_0$), but not to a statistically significant degree. Results in the treatment groups were also substantially worse, and the difference between treated and untreated eyes was insignificant. It is surprising that the pituitary ablation column contains only six eyes in this $N_2F_0H_0$ category, since eyes with extensive neovascularization on the surface of the retina prior to the onset of vitreous contraction would seem to be ideally suited for treatment, either by photocoagulation or pituitary ablation. Perhaps the O'Hare Classification has been misinterpreted and eyes belonging properly in this category have been placed in the $N_2F_1H_0$ category because of fibrous tissue accompanying the new vessels on the surface of the retina. According to the O'Hare Classification, fibrous tissue *on the surface of the retina* is not sufficient to move any eye from the F_0 to the F_1 category, some extension of the fibrous tissue forward

[1] The Yates correction for continuity was used.

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TABLE II.—*Proliferative diabetic retinopathy: Eyes with visual acuity same or better than pretreatment after 1 year or more* [1]

Classification	Total of treated versus untreated eyes								
	(a)		(b)		(c)		(p values)		
	No treatment	Percent	Pituitary ablation	Percent	Photocoagulation	Percent	a:b	a:c	a:b+c
$N_1F_0H_0$ (all)	54/111	50	18/28	64	31/48	65	0.25	0.1	0.05
$N_1F_0H_0$ (U.W. & Kohner)	28/70	40					0.05	0.02	0.005
$N_2F_0H_0$	15/37	41	2/6		20/45	44	>0.9	>0.9	>0.9
$N_1N_2F_0H_1$	10/33	30	5/14		47/85	55	>0.9	0.03	0.05
$N_1N_2F_1H_0$	13/36	36	10/18		23/36	64	0.3	<0.05	<0.05
$N_1N_2F_1H_1$	8/39	21	19/40	48	39/85	46	0.02	0.02	0.01
$N_1F_2H_0H_1$	12/29	41	30/53	57	7/14		0.2	0.8	0.3
$N_2F_2H_0H_1$	11/44	25	67/110	61	44/97	46	0.001	0.05	0.002
Total	123/329	37	151/269	56	211/410	51			
All but $N_1F_0H_0$	69/218	32	133/241	55	180/362	50			

p = 0.013; p = 0.63; p = 0.004; p = 0.3; p = 0.08; p = 0.5

[1] The numerator of each fraction is the number of eyes maintaining visual acuity the same as or better than pretreatment at their last observation. The denominator is the total number of eyes followed 1 year or more.

into the vitreous being required. There is a sufficient number of photocoagulated eyes in the $N_2F_0H_0$ category for comparison with the controls, and it is apparent that photocoagulation did not improve the outlook in this category. While failing to maintain pretreatment or better visual acuity in a significantly higher percentage of eyes than was the case in the control group, it is possible that photocoagulation may have lessened the incidence of the severe degrees of visual loss commonly observed in untreated eyes. In order to test this possibility, we examined the data again, choosing maintenance of 20/200 or better visual acuity instead of pretreatment or better acuity as the criterion for "success." Again there was no significant difference, 32 of 45 (71 percent) photocoagulated eyes and 24 of 37 (68 percent) control eyes retaining 20/200 or better visual acuity at their most recent visit.

As expected, the addition of vitreous hemorrhage in group N_1 N_2 F_0 H_1 made the prognosis worse (although not to a statistically significant degree) in the control group. No difference was found between the pituitary ablation group and the controls, but photocoagulated eyes in this category did significantly better than the controls.

In the N_1 N_2 F_1 H_0 and N_1 N_2 F_1 H_1 categories, fibrous tissue extending forward into the vitreous cavity is present, and we may conclude that retinopathy has entered the stage of vitreous contraction. Eyes in the N_1 N_2 F_1 H_0 category presumably have less severe vitreous contraction and/or less extensive vitreo-retinal adhesions, accounting for the lack of vitreous hemorrhage, and we might expect their prognosis to be better than that of eyes in the N_1 N_2 F_1 H_1 category. In the N_1 N_2 F_1 H_0 category, photocoagulated eyes did significantly better than the controls. The pituitary ablation group also did better than the controls, but not to a significant degree. In the N_1 N_2 F_1 H_1 category, as we might expect, the outlook for eyes in the control group is worse, only eight of 39 (21 percent) eyes maintaining initial or better visual acuity. This represents a significant ($p=0.004$) worsening of prognosis in comparison with the N_1 F_0 H_0 category. Treated eyes in this category, whether in the pituitary ablation or photocoagulation group, had a significantly more favorable outcome than did the untreated eyes.

The N_1 F_2 H_0 H_1 category contains eyes in the last stage of proliferative retinopathy, in which fibrous proliferation overshadows new vessels. Some of these eyes presumably have already entered the phase of remission; and it is, therefore, not surprising that the outcome in the control group was better than in the preceding category and the difference between control and treatment groups insignificant.

The N_2 F_2 H_0 H_1 category is made up of the most severe cases, and, as expected, the prognosis for untreated eyes was poor. Results in both

treatment groups were significantly better than in the control group, and the 67 of 110 eyes retaining vision in the pituitary ablation group represent a significantly ($p=0.04$) better result than the 44 of 97 eyes doing so in the photocoagulation group. If this difference is in fact due to the treatment and not to differences in selection of patients, application of the O'Hare Classification, and/or handling of the data, then it is of considerable importance in the management of diabetic retinopathy, suggesting that these far advanced cases do better with pituitary ablation than photocoagulation. There is, however, a possibility that the patient groups dealt with differed in at least one important respect, namely, the severity of systemic diabetic angiopathy. Most authors reporting on pituitary ablation specified certain minimum requirements in regard to renal function and cardiovascular status, while no such selection was carried out in the photocoagulation series. Data on the renal and cardiovascular status of patients in the photocoagulation series were not available to us, but study of our own patients in the N_2 F_2 H_0 H_1 category showed no difference in results between the 10 eyes of patients who met the usual requirements for pituitary abation and the 16 eyes of patients who did not. The necessity for caution in interpretation of these findings is also apparent when the careful study of Bradley and Rees (Cr. 17) is considered. These authors found that only 42 to 47 percent of all patients subjected to pituitary ablation (without regard to the OHare Classification), retained pretreatment or better visual acuity—a result obviously not significantly different from the photocoagulation results listed in table II for the N_2 F_2 H_0 H_1 category.

Another consideration regarding patient selection in the untreated group in categories more severe than N_1 F_0 H_0 is the probable inclusion of cases too severe for selection into any of the treatment series. This would tend to increase the difference between the control and treated series and might lead to an erroneous conclusion of benefit from treatment. In an attempt to examine this possibility more closely, we selected all eyes with initial vision of 20/40 or better from the groups listed in table I. We chose as the criterion of "success" retention of 20/40 or better visual acuity at the most recent visit. Thus, an eye with initial acuity of 20/15, 20/20, 20/30, or 20/40 was considered a "success" if its final vision was 20/40 or better. The results are listed in table III. Unfortunately the cases of McMeel and coworkers could not be included because of the lack of raw data. In table IV the various series have been pooled according to type of treatment. As is obvious from inspection of table IV, the treated eyes did no better than the controls except in the N_1 N_2 F_1 H_1 category, where the photocoagulated eyes did significantly better than the controls ($p=<0.01$). In this category the eyes of patients subjected to pitui-

TABLE III.—*Proliferative diabetic retinopathy: Eyes with visual acuity 20/40 or better maintaining 20/40 or better after 1 year or more* [1]

	No treatment				Pituitary ablation				Photocoagulation					
First author	Myers	Dobree	Okun	Kohner	Kjellberg	Hardy	Pearson	Roth	Mortimer	Harris	Larsen	Dobree	Okun	Wetzig
CLASSIFICATION														
$N_1F_0H_0$	22/32	9/13	13/17	12/20	5/5	3/3	5/6	1/1	0/1	1/1	6/7	3/4	7/12	6/6
$N_2F_0H_0$	9/17	1/2	3/4	4/4	0/3	0	0	0	0	0	1/3	1/4	8/14	0/1
$N_1N_2F_0H_1$	4/9	0	4/5	0	0/1	0	2/7	1/1	3/4	0	0	0/1	11/17	10/11
$N_1N_2F_1H_0$	5/6	2/8	2/3	2/6	3/6	1/1	0	2/2	0	1/3	2/3	5/5	3/6	5/5
$N_1N_2F_1H_1$	1/9	0/1	0/2	0	5/9	0	1/3	1/2	1/1	2/2	0	0	6/14	8/11
$N_1F_2H_0H_1$	2/5	4/4	0	0	6/9	0	1/4	0	0	2/2	0	2/2	0	1/2
$N_2F_2H_0H_1$	4/7	0	0	0	4/12	1/1	0	0	0	1/2	0/1	0/3	2/7	8/14

[1] The numerator of each fraction is the number of eyes retaining 20/40 or better visual acuity at their last observation. The denominator is the total number of eyes with 20/40 or better initial visual acuity followed 1 year or more.

tary ablation also did better than the controls, but not to a statistically significant degree ($p=0.06$). The similarity of the results in the control series to those reported by Beetham (*1*) is striking.

It is of interest to compare the total eyes in the control, pituitary ablation, and photocoagulation groups in table IV with the comparable figures in table II. It is obvious that the greatest difference between the two tables is in the control group, where the prognosis is improved from 37 percent for all eyes to 59 percent for eyes with initial acuity of 20/40 or better. Even when the N_1 F_0 H_0 category, which probably contains some eyes with retinopathy too mild for selection into any treatment series, is excluded, there remains a substantial difference, 32 percent versus 51 percent. The photocoagulation groups show a similar but smaller difference, but in the pituitary ablation group the prognosis appears the same or even worse for eyes with initial visual acuity of 20/40 or better than for the group as a whole. This paradox is probably explained chiefly by the exclusion of the relatively favorable results of McMeel and coworkers from the 20/40 or better initial visual acuity group because of the lack of raw data. Some increase in the percentage of eyes retaining vision would be expected in table IV, since the criterion of success chosen (maintenance not of pretreatment acuity but of 20/40 or better) is less strict. The markedly greater difference in the control group, however, tends to confirm our suspicion that the differences between control and treated groups in table II are due, at least in part, to differences in the selection of patients. This should not be too surprising, since virtually all authors reporting results in pituitary ablation emphasize careful selection of patients and require "macular vision" in at least one eye, while in the larger part of the "control" series no selection was carried out in regard to visual acuity.

TABLE IV.—*Proliferative diabetic retinopathy eyes with visual acuity 20/40 or better maintaining 20/40 or better after 1 year or more* [1]

Classification	Total of treated versus untreated eyes					
	No treatment	Percent	Pituitary ablation	Percent	Photocoagulation	Percent
$N_1F_0H_0$	56/82	68	14/15		23/31	74
$N_2F_0H_0$	17/27		0/3		10/22	
$N_1N_2F_0H_1$	8/14		3/9		24/33	
$N_1N_2F_1H_0$	11/23		6/9		16/22	
$N_1N_2F_1H_1$	1/12		7/14		17/28	
$N_1F_2H_0H_1$	6/9		7/13		5/6	
$N_2F_2H_0H_1$	4/7		5/13		11/27	
Total	103/174	59	42/76	55	106/169	63
All but $N_1F_0H_0$	47/92	51	28/61	46	83/138	60

[1] The numerator of each fraction is the number of eyes retaining 20/40 or better visual acuity at their last observation. The denominator is the total number of eyes with 20/40 or better initial visual acuity followed 1 year or more.

Unfortunately, therefore, at the end of this analysis, we find ourselves in just about the same position as we were on beginning it. The data suggest but do not prove that pituitary ablation and photocoagulation may be beneficial. Certainly the difference between control and treated groups is not so great as to preclude on moral grounds experimental design that includes random selection of alternate patients into treatment and control groups.

SUMMARY

The raw data of all participants providing it has been compiled, divided into three groups—untreated, pituitary ablation, and photocoagulation—and the outlook for retention of pretreatment visual acuity compared within the various categories of the O'Hare Classification. In all categories except N_2 F_0 H_0 and N_1 F_2 H_0 H_1, eyes in both the pituitary ablation and photocoagulation series appeared to do better than those in the control series. In the N_2 F_2 H_0 H_1 category pituitary ablation appeared perhaps to be superior to photocoagulation. When comparisons were limited to eyes with 20/40 or better visual acuity initially, with maintenance of 20/40 or better acuity chosen as the criterion of success, the differences between treated and control eyes in all but the N_1 N_2 F_1 H_1 category became insignificant. It was concluded that the clinical usefulness of both pituitary ablation and photocoagulation remains unproven by this analysis. Random selection of patients into treatment and control groups in clinical investigation of these treatment modalities appears to the authors to be morally justifiable and scientifically essential.

Reference

1. Beetham, W. P.: *Visual* prognosis of proliferating diabetic retinopathy. Brit. J. Ophthal. 47: 611–619, October 1963.

Epilogues

EPILOGUE 1

Review of Selected Aspects of Diabetic Retinopathy

ROBERT F. BRADLEY, M.D.

This symposium has established surprisingly uniform agreement concerning many problems in diabetic retinopathy:

(1) Great variation in the rate and degree of progression of hemorrhagic or angiopathic retinopathy is readily demonstrated, depending upon the degree of changes in various components at the time observation is begun. Much less variation in the course of retinopathy is noted for comparable degrees of component change. In general, even less variation is apparent with more advanced changes, for example at the $N_2F_2H_2$ stage by the O'Hare classification,[1] than for comparable lesions at an earlier stage; i.e. $N_1F_1H_0$.

(2) Classification of retinopathy components is essential if valid observations concerning natural course and the effects of treatment are to be recorded. The O'Hare Classification has proven the value of simple terminology, in that a simple "lingo" facilitates communication among investigators. The classification needs some revision because the categories are too broad, but addition of further stages of change must not sacrifice too much of the simplicity inherent in the O'Hare system.

(3) Fluorescein angiography provides important information as to areas of capillary closure, neovascularization, and leakage of blood vessels, particularly at earlier stages of angiopathic retinopathy, not provided by standard fundus photographs. The technique serves as an additional means of evaluating the natural and posttreatment course of retinopathy.

(4) Vitreous studies provide the ophthalmologist with further prognostic data through demonstration of red cells and new vessels in the vitreous as well as vitreous contraction. Such studies are an important part of classification and will be of great technical help in guiding the decision for or against photocoagulation and the way in which it is used.

(5) Pituitary ablation favorably alters the course of angiopathic retinopathy in the majority of properly selected patients, but persisting unresolved difficulties remain in avoiding treatment of patients with changes too advanced to be benefited or too early to warrant their being subjected to the medical risks.

[1] O'Hare Classification, p. xxi.

(6) Pituitary ablation remains experimental in that further information concerning the mechanism of its effect is needed, as well as clearer definition of the patient who will not spontaneously improve or respond to photocoagulation.

(7) Photocoagulation is being used at all stages of angiopathic retinopathy and, as such, is clearly experimental. Although no hazard to the patient as a whole, xenon arc photocoagulation poses certain ocular risks which are justified in the more advanced stages of the disease based on the longer term experiences reported by Wetzig and Jepson (ch. 49), Okun and Johnston (ch. 42), and Thornfeldt (ch. 45).

Ruby laser photocoagulation has been of value primarily in earlier stages of angiopathic retinopathy (Zweng, ch. 50, Aiello *et al.*, ch. 35). Virtually no ocular complications are produced. However, it cannot be used directly to obliterate new vessels or hemorrhage. The persistence of beneficial effects following treatment has yet to be established. Possible trial of light coagulation with other wavelengths, especially in the green spectrum, appears worthwhile.

"Better control" of diabetes has been associated with a reduced chance of developing retinopathy according to the two reported studies. The first of these by Caird (ch. 11) based on observations in nearly 2,000 patients revealed: (1) In patients under age 30 at diagnosis of diabetes, retinopathy occurred less frequently in association with lower degrees of glycosuria than among patients in whom glycosuria was consistently high. The lower percentage of glycosuria was associated roughly with a postponement by 2.5 years of the development of retinopathy; (2) For those between age 30 and 60 at diagnosis who had only microaneurysms, more severe "background" retinopathy, or retinal hemorrhages and exudates, the progression or regression of these lesions could not be correlated with lesser or greater amounts of glycosuria; (3) Among 299 patients studied for a period of 10 to 14 years from before until after the development of diabetic retinopathy, a highly significant correlation was shown between frequency of retinopathy and percentage of glycosuria throughout the period of observation and also in the first period of 3 to 7 years (average 4.8), thus appearing to confirm the importance of better diabetic control during the first few years of diabetes.

The second series of observations by Kohner, Fraser, Joplin, and Oakley (ch. 13) is a preliminary report of a prospective study relating the progress of established diabetic retinopathy to diabetic control in a group of 104 patients studied between 1965 and 1968. The followup period of 22 months revealed that "very good diabetic control" appeared to protect patients from worsening of microaneurysms, hemorrhages, and neovascularization; whereas worsening of ex-

udates occurred in the "very good" and "good control" groups with no changes in those with less adequate control. Retinitis proliferans deteriorated irrespective of diabetic control. Although some remissions in all retinopathy features occurred at times, regardless of change in diabetic control, the most striking remissions in the components cited above occurred in patients whose control was the worst prior to entering the study and who, therefore, showed the greatest overall improvement in control during the study.

Discussion pointed out the problems attendant upon the use of an arbitrary glycosuria percentage as an index of control in Caird's study and the need for longer period of followup observations with some additional patients in the study of Kohner *et al.* However, both studies suggested a positive correlation between improved control of diabetes and a reduced chance of developing retinopathy.

All current surgical methods of pituitary ablation including stalk section (Field, McMeel, Sweet, and Schepens, ch. 20; Bradley and Rees, ch. 17) usually produce lasting "moderate" to "maximal" hypopituitarism. Radioactive yttrium pituitary implants have produced degrees of hypopituitarism that can be graded according to the dosage used (Oakley, Joplin, Kohner, and Fraser, ch. 27).

Heavy particle pituitary suppressive therapy utilizing 8,000 to 15,000 rads (Linfoot, Garcia, Chong, Tobias, and Lawrence, ch. 24) results in partial pituitary destruction (estimated at 25 percent by morphologic study), demonstrable primarily by a fall in insulin requirement and a blunting of growth hormone release beginning 2 months after treatment and developing fully in 9 to 16 months. Lesser degrees of reduction in adrenal and thyroid function were found, with only 4 out of 26 juvenile-type diabetics requiring replacement therapy. Following heavy particle irradiation of the pituitary, all parameters of target organ function required a year or more for full development of the indicated degree of suppression. Pituitary suppression by proton beam irradiation has also produced less complete pituitary ablation than is induced by surgical means, with frequent delays in development of hypopituitarism of from a few to 9 or more months following treatment. According to the authors of the latter study (Kjellberg, McMeel, McManus, and Koehler, ch. 23), inadequate hypopituitarism accounted for 9.2 percent of the visual failures among the 152 patients in this study.

In all studies, the simplest means of estimating significant hypopituitarism have been: insulin requirement among insulin-dependent patients (to less than 50 percent of the pretreatment dose on a comparable diet), cessation of menses in menstruating females, and disappearance of urinary FSH. Growth hormone response to insulin-

induced hypoglycemia or arginine infusion has been used in some patients. However, by radio-immunoassay techniques, growth hormone has not been eliminated completely with the consistency predictable from traditional observations of ease of removal of this parameter of pituitary function. The thyroid has been the most consistent target organ comprehensively evaluated in all studies, with consistent loss of function in those patients rated as having "maximal" or "complete" hypopituitarism. However, some tests of thyroid function remained normal or only partly suppressed in many patients treated surgically and in a considerably larger number treated by pituitary radiation with heavy particles or proton beam. Plasma ACTH, adrenal responsiveness to metapyrone suppression, omission of adrenal steroid replacement with studies of endogenous adrenal function, and plasma TSH have been done in too few instances to quantitate lesser degrees of residual pituitary function. In general, all patients having surgical pituitary ablation required adrenal steroid replacement, and most had sufficient hypothyroidism to warrant replacement treatment. Few of the patients having heavy particle or proton beam pituitary irradiation required hormone replacement, with variation depending on the amount of radiation delivered and the length of time after treatment.

Marked versus little or no pituitary ablation is accurately delineated for clinical purposes by change in insulin requirement, cessation of menses, demonstration of dependence upon adrenal steroid therapy, and the usual tests of thyroid function such as PBI, T_3 uptake, RAI uptake, etc. However, more exhaustive testing to determine precise quantitative losses of pituitary or target organ hormones is desirable if further knowledge of the mechanism by which ablation of pituitary function produces regression of angiopathic retinopathy is to be gained.

Patients undergoing pituitary ablation by any procedure should have identification indicating (1) their extreme sensitivity to administered insulin, and (2) steroid dependence with the need for prompt and aggressive replacement therapy during acute illness.

Difficulties in assessing sexual function before and after pituitary ablation are evident in all experiences. In general, some loss apparently occurs despite adequate androgen or estrogen replacement, tending to be greater in those with preexisting diminution in sexual function.

Although truly prospective data in matched controls not subjected to pituitary ablation is available in only one study (Lundbaek, ch. 25), there seems to be agreement that pituitary ablation produces remission in certain components of angiopathic retinopathy more rapidly and with greater frequency than occurs in untreated individ-

uals. The components primarily responding are hemorrhage, neovascularization, and to some extent venous abnormalities. "Moderate" to "maximal" pituitary ablation appears more likely to produce the desired effect. Comparably favorable ocular results in patients treated with heavy particle irradiation are not clearly related to the fact that a lesser degree of pituitary ablation is effective, as these patients had earlier stages of retinopathy. Patients treated by proton beam irradiation, in most instances, had eye lesions comparable to those found among surgically treated patients, and the eye results appear much the same as for surgical procedures. Nonetheless, Kjellberg *et al.* have emphasized the trend toward less favorable visual results among patients whose pituitary ablation is less complete or in whom it is delayed.

Medical management for patients undergoing surgical pituitary ablation has been the same in principle, with variations related to individual preference for smaller or larger doses of parenteral cortisol treatment and the use of insulin. The rapid fall in insulin requirement after the first few days of the postoperative period when steroid dosages are rapidly reduced requires skill and caution. The occasional marked retention of water noted in patients during the second half of the first week postoperatively requires alertness if cerebral edema and other evidences of water intoxication are to be avoided. An abrupt fall in urinary output with a rise in urinary specific gravity provides early warning of the problem. Treatment consists of water restriction, avoidance of pitressin administration, and possibly the administration of salt or an increase in steroid replacement dosage if previous sodium losses have been excessive. The mechanism of the water retention with dilutional hyponatremia is presumed to be that of an abrupt release of ADH from degenerating neurohypophyseal fibers.

Administration of pitressin for diabetes insipidus is either unnecessary or only temporarily required if precautions have been taken to preserve the hypophyseal stalk and to avoid injury to the posterior pituitary lobe. (Hardy et al., ch. 22).

Pituitary ablation reduces renal function, reportedly reversible by the administration of growth hormone. Limited observations suggest questionably favorable effects upon certain components of glomerulosclerosis as demonstrated by the electron microscope. No significant effects upon neuropathy or other vascular lesions of diabetes have been shown. In one study based on preoperative renal biopsies, a significantly positive correlation was found between the degree of hyaline degeneration of the hilar glomerular arterioles with a less favorable ultimate clinical outcome in regard to retinopathy (Field, McMeel, Sweet, and Schepens, ch. 20).

Overall mortality at 5 or more years has been less than 40 percent in all series. Most deaths have occurred as a result of vascular lesions—coronary, renal, and cerebrovascular.

EPILOGUE 2

Summary of Personal Impressions of Airlie House Symposium on Diabetic Retinopathy

MATTHEW D. DAVIS, M.D.

The goal of the symposium was threefold: to promote communication at the personal level between clinical investigators and practitioners interested in the treatment of diabetic retinopathy; to assemble data from many centers on which to base objective conclusions regarding the merits of pituitary ablation and photocoagulation; and, finally to work out a mutually agreeable classification of diabetic retinopathy which might be applied in reasonably objective fashion in future studies and which might allow valid comparisons to be made between various types of treatment at different centers.

Given the magnificent facilities of Airlie House, the generous support of the Public Health Service, the diligent work of Drs. Fine and Goldberg and the enthusiasm with which the proposal for the conference was received by the participants, the achievement of the first goal was assured.

Prior to the conference, the second goal seemed more likely of achievement than the third. By now the reader is aware, however, that to the disappointment of all, no clear-cut consensus regarding pituitary ablation and photocoagulation has resulted from the conference. Some of the probable reasons for this have been outlined in chapter 58. We are most pleasantly surprised, however, to report that the outlook for general acceptance of the classification presented in chapter 2 seems very good. If this classification does indeed find wide acceptance, this alone would be ample justification for all the time and effort that went into the symposium.

Although no consensus was reached concerning pituitary ablation and photocoagulation, certain subjective impressions did result, and it seems unfair not to share these with the reader. First, the notion that photocoagulation may have some mysterious general effect on untreated areas of the retina was, perhaps unexpectedly, strengthened. The reports of Wessing and Meyer-Schwickerath (ch. 48) and of Aiello and coworkers (ch. 35), although uncontrolled and speculative, nevertheless offer hope that early, mild photocoagulation applied to high risk patients with very early proliferative diabetic retinopathy or even severe preproliferative retinopathy may prevent development of severe proliferative disease. If this indeed proves to be the case, it will be extremely important to develop criteria for recognition of "high risk" eyes, since, as the report of Caird (ch. 3) has demonstrated,

the overall prognosis for nonproliferative diabetic retinopathy is very good (if one selects for study all patients with any degree of ophthalmoscopically recognizable lesions).

Another most encouraging finding is the apparent ability of photocoagulation applied to paramacular microaneurysms and other vascular abnormalities to favorably influence macular edema. The reports of Welch (ch. 47), Cleasby (ch. 36), Mortimer (ch. 41), and Okun (ch. 42) are all in agreement in this regard, and we too have had similar experience. When one considers the very large number of adult onset diabetics who lose reading vision from macular edema, recognition of the possibility of effective therapy is of great importance.

Finally, although a large, rigidly controlled series of patients subjected to pituitary ablation for diabetic retinopathy still does not (and probably never will) exist, the findings of Joplin *et al.* (ch. 27) and the continuing enthusiasm of other highly qualified clinicians in many centers for this procedure, even after 5 and more years of experience, are strongly suggestive that pituitary ablation does indeed favorably influence proliferative diabetic retinopathy in some patients. The small fraction of the population afflicted with symptomatic retinopathy which is suitable for pituitary ablation and the difficulty of predicting even among these patients which ones require and will benefit from the procedure continue to limit its usefulness. The succinct conclusion of Rucker that "Our data suggests that of each three patients subjected to section of the stalk of the pituitary, one would have retained good vision without the operation, one lost vision in spite of it and one probably retained vision because of it" (*1*) is probably close to the truth and certainly is not overly pessimistic regarding the value of pituitary ablation. If the current promise of "preventive" photocoagulation proves valid, the question of the efficacy of pituitary ablation may become academic.

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[1] Rucker, W. C. et al., Effect of section of pituitary stalk on diabetic retinopathy, Proc. Mayo Clin. 42 : 409–416 (July), 1967.

Photocoagulation for Diabetic Retinopathy

EDWARD OKUN, M.D.

It was agreed by all participants experienced with photocoagulation that this type of therapy can eliminate areas of neovascularization from the diabetic eye. Early proliferative disease is more effectively treated than the advanced stages of proliferative diabetic retinopathy. The most difficult areas to treat are neovascularization of the disc itself and intravitreal microangiopathy. The prognosis is considerably poorer in eyes with significant vitreous hemorrhage and in those with extensive intravitreal proliferation.

Photocoagulation of paramacular neovascularization and leaking intraretinal capillaries leads to less macular edema with improvement of macular function in some cases.

Extensive photocoagulation has resulted in a major change in the appearance of the fundus in some patients. These changes consist of: (1) decrease in venous distension, (2) decrease in arterial caliber, (3) cessation of neovascularization, and (4) partial optic atrophy.

Photocoagulation therapy aims to prolong the life of the diabetic eye by: (1) directly eliminating the fragile, new-formed vessels which are known to leak into the vitreous, (2) decreasing the rate of neovascularization by eliminating abnormal retinal tissue, and (3) inducing chorioretinal adhesions which will counteract vitreoretinal traction forces and avoid retinal detachment.

The major complications of therapy were: (1) retinal detachment (2) traction hemorrhage, (3) maculopathy, (4) accidental macular burn, and (5) venous or arterial occlusion. Most of these complications could have been avoided, since they represent either overtreatment or misplaced treatment.

The ruby laser is not as effective an instrument as the xenon arc for the purpose of directly eliminating surface neovascularization. Its advantages are that no anesthesia is required, and less energy is required to produce a deep lesion. Preliminary reports of its indirect effectiveness in eliminating surface neovascularization must await further studies.

The main areas of difference in opinion seem to be in the selection of cases for therapy, the amount of coagulation performed at one sitting, and the value of fluorescein as an adjunct to treatment. Most of those reporting to this symposium did not undertake therapy in nonproliferative (background) retinopathy, since it was their opinion

that very few of these eyes get into serious trouble without any therapy. The very advanced cases with marked fibrous proliferation were treated by only a few of the investigators. Some felt that very little treatment should be carried out at one sitting, and that multiple treatments were less apt to cause vitreous shrinkage. Those that favored extensive therapy at one sitting argued that an intervening vitreous hemorrhage could prevent completion of therapy. Another point of controversy was the treatment of traction-type hemorrhages. Most felt that these areas should be photocoagulated. Those that favored fluorescein during treatment argued that more areas of neovascularization could be detected and more effectively treated. Those that argued against its routine use felt that the vitreous could be overheated due to its diffusion into the vitreous.

The major deficiences uncovered at this symposium were: (1) the difficulty of comparing cases selected for treatment, as well as effects of therapy, because of the lack of an adequately detailed classification of proliferative diabetic retinopathy; (2) lack of more controlled studies on effectiveness of photocoagulation, particularly in early cases (only one study, thus far, has proven the effectiveness of photocoagulation in decreasing the rate of progression of diabetic retinopathy, Okun); (3) the inability to identify prognostic signs in cases of nonproliferative retinopathy which would allow one to select proper cases for prophylactic treatment; (4) lack of expert ophthalmologic evaluation, pre- and post-treatment, including stereoscopic fundus photographs, total fundus sketches, and biomicroscopic examination of the vitreous.

The best available therapy for any specific case of proliferative diabetic retinopathy can be determined only by a well planned study, in which similar conditions are treated by different techniques.

For proper selection of cases, treatment, and unbiased evaluation, I would suggest a cooperative study in which case selection is based upon a mutually acceptable classification scheme. Case selection and followup studies would include, in addition to functional studies, stereoscopic photography, fluorescein photography, fundus drawings, and biomicroscopic study of the vitreous cavity.

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EPILOGUE 4

Production of Hypopituitarism in the Treatment of Diabetes

WILLIAM H. SWEET, M.D., D. Sc.
RICHARD A. FIELD, M.D.

The early thought of Luft and Olivecrona (1955) that hypophysectomy might ameliorate quite a number of the lesions of the diabetic has proven largely a vain hope (*1*).

Systemic disease: In Poulsen's famous original patient (*2*, *3*), whose adenohypophysis was virtually totally destroyed for about 15 years, the post mortem findings included advanced athero- and arteriolosclerosis in many organs including the heart and kidneys. In addition the renal glomeruli were hyalinized, and there was lymphocytic infiltration of the interstitial renal tissues. "The retina was the only organ which showed less advanced derangement than might have been expected."

There are intimations, however, that the renal disease may occasionally improve after pituitary ablation. Thus Hernberg *et al.* (*4*) were tentatively encouraged about this possibility, and Luft (*5*) saw indications of this in one of his five patients with renal disease before hypophysectomy, all of whom, however, died in renal failure. In the more sophisticated studies of Ireland *et al.* (*6*), electron micrographs of renal biopsies in four patients before and 1 to 2 years after hypophyseal stalk section or effective Yttrium-90 implant suggested that the thickened capillary basement membrane in the glomeruli was reduced in thickness after operation in all four. This reduction exceeded the standard deviation of the measurements in only one of them. There was, in addition, after pituitary destruction, "striking restoration of the normal structure of the nuclei and cytoplasm of the mesangial cells and a great increase in the cytoplasm of the atrophic endothelial cells." There was no improvement in the arteriolar lesion. Ray *et al.* (*7*) comment that some of their patients with moderately impaired renal function before hypophysectomy have shown no progession of this disease in a 3- to 7-year followup. These fragmentary data are presented to remind the investigator that a continuing study in this area may prove rewarding.

Retinal exudates and fibrous proliferation: With respect to the retina, there is general agreement in this symposium that the diabetics' hard exudates and fibrous proliferation do not respond well to any form of pituitary suppression studied to date. However, in one of our

early accounts (*8*), we described condensation and attenuation with increased translucency of proliferative "glial tissue" and migration of exudates outwards from the macular region. In the 8 patients of Pearson *et al.* (*9*) absorption of hemorrhages and exudates was also described. However Oakley *et al.* (ch. 29) point out that they have seen hard exudates come and go at random without correlation with the endocrine status. We recorded (ch. 20) a decrease of fibrous proliferation clearcut enough to improve the rating in the O'Hare Classification [1] from F_2 or F_1 toward F_0 in 21 eyes or 14 percent of those rated before and after stalk section. In the control studies from the groups at Aarhus and at Hammersmith, no data have been published as yet in which exudates and fibrous proliferation are compared in the treated and untreated groups, and the numbers of patients from the other centers showing improvement are too small to permit conclusions as to the significance of the findings. However, as Joplin *et al.* (*10*) point out, pituitary suppression might prevent the appearance of fibrous retinitis proliferans "in the young diabetic with active retinopathy who is otherwise particularly likely to develop this condition." There are as yet no clearcut data on this latter score.

Retinal vascular disease: We are left with the various features of angiopathic retinopathy [2] as the only ones for which pituitary destruction seems to be helpful. At a similar symposium in 1962 (Diabetes, vol. 11, November–December 1962) it was the improvement or arrest of this type of retinopathy in 75 of the 119 survivors of pituitary surgery which led to the more widespread intensive appraisals of the last 6 years along with improved tactics for achieving the desired results. The complete mystery as to the features of hypothalmo-hypophyseal function which must be altered in order to improve the retinal lesions has given logical scope for studies of partial as well as total hypophyseal lesions.

Nonrandomized studies: The first extensive series of such lesser lesions was that of our group with stalk sections. Documentation by serial examination of progressive angiopathy (indeed, to the point of blindness in one eye of 74 percent of the patients) was a prerequisite to surgery. One of us (W. H. S.) regarded the effects of stalk section as likely to be little more than those of a sham operation involving craniotomy. Hence, it was with amazement that he watched his ophthalmic and medical associates record the prompt and striking changes for the better in so many of the aspects of preoperative retinal disease, as noted in the first three patients (Field *et al.* (*11*)), in the first eight patients (Contreras *et al.* (*12*)), and in the first 13 patients (Field *et al.*

[1] O'Hare Classification, p. xxi.

[2] Editor's Note.—The term "angiopathic" refers to the vascular, nonfibrous components of the retinopathy.

(*8*)). His eagerness to proceed to the "real operation" of hypophysectomy, on the one hand, or to a randomized study, on the other hand, was quashed by the invariable assurance from less involved ophthalmologists that these results could not be due to chance. None of them had ever seen three successive advanced cases, much less 13, show spontaneous improvement. Qualms have arisen in our minds as to the advisability of our carrying out a randomized study after exhortations by our colleagues to do so on general grounds. However, when the same colleague, confronted by the specific problem of his own patient rapidly going blind, refers him to us for prompt operation, these qualms tend to be allayed. We assume that similar thoughts have passed through the minds of those in several of the other hypophyseally oriented groups represented in this volume who have not done controlled studies.

The encouraging early results have become even more significant as they have been sustained over the years. As McMeel points out in his summary (ch. 32), every one of the 11 groups reporting here found that the angiopathic aspect of the retinopathy responded well to pituitary ablation. Particularly convincing to us are the studies of Behrendt, Field, and Duane (*13*) on the frequency of occurrence of the "involutional phase" of the active angiopathic disease in the 18 stalk-sectioned patients they examined. This phase is characterized not only by cessation of neovascularization but also by involution as well, with only dense, shrunken, avascular, fibrotic strands remaining. All of the 18 patients had had the surgery over 2 years before, and 16 of them were now in such as involutional phase. These ophthalmologists had seen such involution occur spontaneously in only one case, an experience similar to that of Beetham (*14*) who reported only eight such spontaneous involutions out of 351 patients. Moreover, this correlates well with the numerous fluorescein studies which reveal a diminution in the abnormal retinal vascular permeability to this dye following induction of pituitary lesions (ch. 16).

Controlled clinical trials: Such studies are much more convincing to the man who has not observed the spectacular temporal sequence of improvement so often occurring right after hypophyseal surgery. They clearly play a vital role in determining the rate of acceptance or rejection of this or any other new form of therapy. Although one is reluctant to sacrifice so important a function as eyesight in an effort to obtain statistically valid data, the eloquent persuasiveness of such data will result in saving vision in more eyes if it turns out in one direction, or save more people from needless surgery if it points in the other direction.

The two controlled studies reported to us have a worldwide high degree of credibility because of the evident care with which they performed. Lunbaek and his six colleagues (ch. 25) are supplying us with

an ongoing analysis of 15 patients, totally hypophysectomized by the transethmoido-sphenoidal route, matched carefully with 15 patients subjected to no surgery. All 30 have been provided with similarly assiduous control of their diabetes and a full battery of oft-repeated quantitative appraisals of both visual and systemic functions. The 1- to 5-year followup now available reveals that the hypophysectomized group has fared better on these five visual counts: neovascularization, visual acuity, visual field, rubeosis iridis, and hemorrhagic glaucoma. No specific comment is made on the incidence of retinovitreous hemorrhage, venous dilatation, exudates or fibrous proliferation. We shall all be following the further results of this ongoing study.

In the larger series of patients studied from Hammersmith (ch. 27), there have been two important sequential aspects of their controlled trials. There earlier studies (Joplin *et al.* (*10*)) included a randomized series of 12 nonsurgically treated controls and 11 with intrasellar implants of Y^{90}. About half of the implanted patients improved in at least one vascular component of the retinopathy, only those with extensive fibrous proliferation showing deterioration. Vision either remained stable or improved a little. The control series did less well *vis-a-vis* angiopathic retinopathy and visual acuity. These workers continued with an even more convincing series of studies in which patients were given the Y^{90} beta-radiation in three different dose ranges. This provides, in many respects, and even better control group, since the lightly radiated patients have undergone the same manipulations as those with the heavier doses. Moreover, they have set up an excellent graded series of retinal photographic standards of diabetically diseased eyes forming a basis against which not only they, but also the rest of us as well, can compare our treated cases (Oakley *et al.* (*15*)). The degree of hypophyseal hypofunction has been classified into maximal, intermediate, and slight grades according to criteria described in chapter 1. The patients' retinas were studied with respect to: (1) hemorrhages and microaneurysms. (2) new vessels, and (3) venous irregularities. In all three categories, the maximally hypopituitary patients fared better than those in the grades "slight" or "slight and moderate." These results were significant at the .04 level or much better in the last two categories.

The Joslin group have also assembled evidence that small degrees of hypopituitarism following either stalk section without a barrier below the hypothalamus or proton beam therapy were associated with less rapid regression of hemorrhage and new vessels than occurred with a more total hypophysectomy (ch. 17).

However, the Berkeley groups, without giving us their specific data, were surprised to observe that ablative doses to the pituitary of alpha particles were not more effective in stabilizing retinal pathology than

much lower doses (below 15,000 rads), which provided major hypopituitarism in very few patients.

To us it seems proven beyond a reasonable doubt that the establishment of a major degree of pituitary hypofunction is well correlated with improvement in the clinical course of angiopathic diabetic retinopathy, regardless of the effect of more modest degrees of hypofunction.

The critical parameter of hypothalamo-hypophyseal function for retinal improvement: Probably no single feature of the problem has contributed more to the skepticism with which hypophyseal destruction as therapy has been received than the fact that no one understands why it might work. The standard use of thyroid and adrenal replacement therapy after total hypophysectomy without recurrence of the retinal lesions served early to discourage the notion that these are the relevant factors. In agreement with this, Ray *et al.* (*7*) report one patient whose retinopathy was unaltered by adrenalectomy but then strikingly improved after hypophysectomy.

Growth hormone: The finding at post mortem in Poulsen's case of a destroyed anterior lobe and an intact posterior one left principally the growth hormone in the adenohypophysis as the probable guilty substance. This seemed to substantiate an earlier observation of Pearson *et al.* (*16*), who gave small amounts of growth hormone to two of their hypophysectomized diabetics; fresh retinal hemorrhages promptly developed. However, our own more extensive studies of somatotropic growth hormone (HGH) responses in 18 patients revealed that these occurred independently of angiopathic ocular changes. All of the patients were tested for HGH responses to insulin-induced hypoglycemia before and several months after surgery (*17*). Linfoot *et al.* (ch. 24) studied the HGH responses to arginine, and also concluded that they could not implicate growth hormone as either a causative or palliative factor in the angiopathic type of retinopathy. Moreover, very few observers have recorded florid angiopathic retinopathy in any acromegalic. And Kohner, in the discussion of Medical Aspects of Pituitary Ablation in this symposium, said she was unable to detect even an early stage of retinopathy with her fluorescein injections in 15 acromegalics studied both before and after treatment with Y^{90} implants.

Gonadotropins: Neither do retinal events correlate well with the activity of these hormones. We have seen four patients whose hemorrhages in the retina recurred after more than 2 years of remission despite no detectable resumption of secretion of gonadotropins, TSH or ACTH. Conversely, another young woman's excellent remission continued despite resumption of menses after 1 year and a later preg-

nancy (ch. 20). Bradley and Rees (ch. 17) also record four late recurrences of angiopathy and hemorrhage, despite apparent maintenance of the earlier degree of hypopituitarism.

We are left in the unsatisfactory position of not knowing whether success is related to decrease of a hormonal factor in hypophysis or hypothalamus, or to increase of a hypothalamic releasing factor provoked by the lesion, or to a neural mechanism. The latter must be given at least some slight consideration because of the evidence adduced by Wolter and Knoblish (*18*) of efferent unmyelinated fibers in the pituitary stalk passing into the chiasm and both optic nerves and by Wolter (*19*) of "a peculiar proliferation (hyperregeneration) of centrifugal nerves around blood vessels and microaneurysms in advanced diabetic retinopathy."

Value of total hypophysectomy versus other types of pituitary suppression: An inexplicable feature of the reports as they stand at present is the relatively similar percentages of maintenance of visual acuity regardless of the type of interference with the gland. The least destructive procedure, the 8,000 to 15,000 rads of transsellar radiation by the Berkeley group has usually had little effect on thyroid and adrenal function. Yet they say that about 80 percent of their patients maintained visual acuity in at least one eye for 3 to 4 years (ch. 24). Conversely, in probably the most rigidly selected and totally hypophysectomized group reported to us, the last 38 patients of Ray *et al.* (ch. 21), the rate of arrest or improvement in visual acuity was 79 percent in 47 patients followed from 2 to 12 years.

If we take our own patients with stalk section, excluding those over 40 years of age (as Ray did in most of his series), we have 72 followed from 3 to 9 years, 81 percent of whom have maintained or improved their visual acuity. More vitreous hemorrhage was responsible for the failure or regression following operation in 30 percent of our patients. This breakdown as to the cause of a poor result is not available in other series, and is probably important to know.

Thoughts for the future: More accurate comparisons between groups of workers may well reveal less consistency in the visual results than the current figures depict. We certainly need an objective system of comparison transferable from one center to another, and the Hamersmith series (ch. 1) of standard retinal photographs would seem, at the least, to be a good starting point. However, we cannot escape the thought that the similarity between the results of stalk section maintained by a subhypothalamic barrier and those of total hypophysectomy should lead us to analyze the role of hormones or nerves of the posterior and intermediate lobes, of specific hypothalamic substances including the releasing factors, and to search for

mechanisms as yet undescribed to account for the tantalizing and now widely documented retinal benefits in diabetics accruing in some way from maneuvers in and about the sella turcica.

Linfoot *et al.* (ch. 24) and Joplin (discussion of Surgical Aspects of Pituitary Ablation, this symposium) have both pointed out that modest doses of alpha or proton radiation carry so minimal a risk that they are suitable for a randomized or even a double blind study. Patients with only a "mild background retinopathy" of microaneurysms, small intraretinal hemorrhages, exudates and/or venous irregularities would be selected and the whole group followed for years, in the hope of avoiding in the treated cases vitreous hemorrhages and fibrous proliferations with retinal detachment. This seems a particularly valuable type of study at the present stage of our knowledge.

A final comment seems appropriate on the relative places of hypophyseal supression and of focal coagulation of appropriate retinal lesions. We think Ray has put it well when he writes, having listened to the papers presented here, "Such coagulation is comparable to spot treatment of metastatic cancer by X-ray—it has its place" (*20*). However, suppression of pituitary function may cause cancers to regress everywhere in the patient, and in the diabetic it benefits the entire retina, usually arresting or improving the angiopathic retinal disease over the long term. Moreover, the possibility of even wider systemic benefits, notably to the kidneys, is not yet excluded. The low risk maneuvers involved in achieving the pituitary suppression lead us to select this over retinal coagulation as the primary mode of therapy, supplementing this with coagulation as required. This viewpoint seems the more compelling to us in that the procedure has little value in protecting the most crucial retinal area, the macula.

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Appendices

Appendix A

E. M. KOHNER, T. R. FRASER, G. F. JOPLIN, AND N. W. OAKLEY

(DATA FROM CHAPTER 13)

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Mode of therapy	Date of last exam	Duration of follow-up (months)	Visual acuity at last exam	Classification of retinopathy at last exam	Complications
1. I. A.	R	49	F	N	40	47	6/9	B	Lente Ins.	2- 9-68	19	6/9	B	
	L	--	--	--			6/9	B				6/9	B	
2. L. A.	R	53	F	K	47	52	6/6	B	CP 250	12- 8-68	17	6/9	B	
	L	--	--	--			6/6	B				6/9	B	
3. E. A.	R	48	F	N	40	40	6/9	$N_1F_0H_0$	Lente Ins. (Sol+ NPH BD).	11- 2-67	25	6/9	$N_1F_0H_0$	TB.
	L	--	--	--			6/9	B				6/9	B	
4. A. A.	R	48	M	K	44	45	6/6	B	CP 250 Atromid S	8- 1-68	32	6/6	B	
	L	--	--	--			6/6	B				6/6	B	
5. B. A.	R	31	F	K	12	29	6/24	$N_1F_0H_0$	BD SOL+NPH Ins.	9-23-67	11	6/24	$N_2F_0H_0$	Died, renal failure.
	L	--	--	--			6/18	$N_1F_0H_0$				CF	$N_2F_0H_0$	
6. W. B.	R	59	F	K	50	56	6/6	B	CP 250 phenformin	5- 3-68	19	6/5	B	
	L	--	--	--			6/6	B				6/5	B	
7. I. B.	R	57	F	K	49	54	6/6	B	CP 250 phenformin	2-10-68	25	6/6	B	
	L	--	--	--			6/5	B				6/5	B	
8. A. B	R	34	F	K	17	32	6/6	B	BD SOL+NPH Ins.	3- 8-68	22	6/6	B	
	L	--	--	--			6/6	B				6/5	B	
9. J. B.	R	36	M	K	16	35	6/18	B	BD SOL+NPH Ins.	6-16-68	10	6/12	B	
	L	--	--	--			6/12	B				6/9	B	
10. A. B.	R	61	F	K	60	60	6/36	B	CP 250	3- 2-68	10	6/60	B	
	L	--	--	--			6/9	B				6/9	B	
11. H. B.	R	55	F	K	19	50	6/9	B	BD SOL	1- 5-68	26	6/6	B	
	L	--	--	--			6/6	B				6/6	B	

E. M. KOHNER, T. R. FRASER, G. F. JOPLIN, AND N. W. OAKLEY—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Mode of therapy	Date of last exam	Duration of follow-up (months)	Visual acuity at last exam	Classification of retinopathy at last exam	Complications
12. E. B	R	64	M	K	46	51	6/12	B	CP. 500 phenformin	12-31-66	11	6/12	B	Died, valvular heart dis., bronchopneumonia
	L	--	--	--			6/9	B				6/9	B	
13. Bo	R	68	M	K	48	66	6/12	B	BD. Sol	3-15-68	24	6/5	B	
	L	--	--	--			6/6	B				6/5	B	
14. Brad	R	--	F	K	43	43	6/18	B	TOLB	9-30-67	24	6/36	$N_1F_0H_0$	
	L	--	--	--			6/6	B				6/9	B	
15. Brai	R	70	M	K	55	68	CF	B	BD. SOL+NPH	5-24-68	23	CF	B	Congenital amblyopia, R. E
	L	--	--	--			6/6	B				6/6	B	
16. Bri	R	30	M	K	4	26	6/60		BD. SOL+NPH	6- 8-68	23	6/60		Cataracts R: Uveitis
	L	--	--	--			6/5	B				6/5	$N_1F_0H_0$	
17. Bro	R	62	M	K	58	58	6/60	$N_1F_0H_0$	CP. 250	2-10-68	26	6/60	B	
	L	--	--	--			6/36	B				6/24	$N_1F_0H_0$	
18. Bun	R	56	F	K	42	53	6/12	B	BD. SOL+NPH	7- 6-68	6	6/12	B	
	L	--	--	--			6/9	B				6/9	B	
19. Bug	R	--	M	K			6/18	B	BD. SOL+NPH	9- 2-67	6	CF	$N_1F_0H_0$	Died, renal failure.
	L	--	--	--			6/18	B				CF	$N_1F_0H_0$	
20. Ca	R	29	M	K	13	27	6/6	B	BD. SOL+NPH	3- 1-68	16	6/6	$N_1F_0H_0$	
	L	--	--	--			6/9	$N_1F_0H_0$				6/9	$N_1F_0H_0$	
21. Ch	R	67	F	K	55	65	6/9	B	CP. 250	4-19-68	18	6/9	B	
	L	--	--	--			6/6	B				6/6	B	
22. Cl	R	--	M	K	17	29	6/5	$N_1F_0H_0$	BD SOL+NPH	6- 8-68	31	6/9	$N_1F_0H_0$	
	L	--	--	--			6/6	$N_1F_0H_0$	Atromid S			6/5	$N_1F_0H_0$	
23. Cok	R	29	M	K	2	28	PL		BD SOL+NPH	6- 8-68	7	6/5		R. Glaucoma
	L	--	--	--			NLP	$N_1F_0H_0$				6/5	$N_1F_0H_0$	

24. Col	R	53	M	K	27	50	6/6	$N_1F_0H_0$	SOL+NPH/SOL	2-23-68	22	6/5	B	
	L	--					6/6	B				6/5	B	
25. Col	R	68	F	K	66	66	LP	B	Diet only	3- 8-68	16	LP	B	
	L	--					6/5	B				6/5	B	
26. Con	R	31	M	K	18	28	6/6	B	1× daily SOL	6-15-68	20	6/6	B	
	L	--					6/6	B				6/6	B	
27. Coo	R	64	M	K	42	62	6/6	B	Lente	3-22-68	29	6/6	B	
	L	--					6/6	B				6/6	$N_1F_0H_0$	
28. Cou	R	64	M	K	29	57	6/12	B	BD NPH	5-10-68	18	6/12	B	
	L	--					6/9	B				6/9	B	
29. Coz	R	--	F	K	10	27	6/6	B	SOL.+PZI/SOL	5-18-68	27	6/6	B	
	L	--					6/6	B				6/6	B	
30. Cr	R	24	M	K	4	21	6/6	B	BD SOL.+NPH	5- 3-68	81	6/6	B	
	L	--					6/6	B				6/6	B	
31. Dalt	R	42	M	K	35	40	6/6	B	Daily NPH	7-12-68	25	6/6	B	
	L	--					6/9	B				6/12	B	
32. Dal	R	59	F	K	35	55	6/36	B	BD SOL.+NPH	2-16-68	27	6/36	B	
	L	--					6/12	B				6/9	B	
33. Dan	R	60	M	K	56	57	6/5	B	BD NPH	10-13-67	27	6/5	B	
	L	--	--	--			6/5	B				6/5	P	
34. Dar	R	35	M	K	20	32	6/6	$N_2F_0H_0$	BD SOL+NPH	8-30-67	13	6/5	$N_1F_0H_0$	
	L	--	--	--			6/12	$N_2F_0H_0$				6/9	$N_1F_0H_0$	
35. De	R	61	F	K	58	58	6/9	B	Diet	1-12-68	26	6/9	B	
	L	--					6/9	No picture				6/9	No picture	
36. Dro	R	70	M	K	59	70	6/6	B	CP 250 Phenformin	2- 9-68	26	6/6	B	Coronary.
	L	--	--	--			6/6	B				6/6	B	
37. Du	R	57	M	K	49	55	6/9	B	CP 500 Phenformin	2- 3-68	10	6/9	B	
	L	--	--	--			6/9	B				6/9	B	
38. Dra	R	59	F	K	49	56	6/6	B	Lente	1-26-68	25	6/9	B	
	L	--	--	--			6/6	B				6/9	B	
39. Fi	R	70	F	K	56	65	6/9	B	CP 250	11-11-66	20	6/6	B	Died, coronary.
	L	--	--	--			6/9	$N_1F_0H_0$				6/6	B	
40. For	R	61	M	K	58	58	6/18	B	Lente	1-20-68	25	6/24	$N_2F_1H_0$	
	L	--	--	--			6/12	B				6/12	$N_2F_1H_0$	

E. M. KOHNER, T. R. FRASER, G. F. JOPLIN, AND N. W. OAKLEY—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Mode of therapy	Date of last exam	Duration of follow-up (months)	Visual acuity at last exam	Classification of retinopathy at last exam	Complications
41. Fou	R	66	F	K	62	62	6/18	B	CP 250, Atromid S.	9-23-67	23	CF	B	
	L	--	--	--			6/9	B				6/36	$N_1F_0H_0$	
42. Ge	R	--	M	K	26	42	6/6	B	BD SOL + NPH	5-14-68	18	6/6	B	
	L	--	--	--			6/6	B				6/6	B	
43. Gi	R	38	F	K	26	36	6/5	B	BD SOL + NPH	7-18-68	36	6/5	$N_1F_0H_0$	
	L	--	--	--			6/5	B				6/5	B	
44. Gl	R	36	M	K	21	29	6/6	B	BD SOL + NPH	6-15-68	30	6/6	B	
	L	--	--	--			6/6	B				6/6	$N_1F_0H_0$	
45. Go	R	66	F	K	54	60	6/6	B	Tolbutamide 0.5 BD	1-12-68	30	6/5	B	
	L	--	--	--			6/6	B				6/9	B	
46. Fr	R		F	K	20	29	6/9	$N_1F_0H_0$	BD SOL+NPH	10-14-67	24	6/60	$N_2F_2H_0$	
	L	--	--	--			6/18	$N_1F_0H_0$				6/36	$N_2F_1H_0$	
47. Ha	R	37	M	K	17	32	6/9	B	BD SOL+NPH	7- 5-68	24	6/5	B	
	L	--	--	--			6/9	B				6/5	B	
48. He	R	--	F	K	5	14	6/6	$N_2F_0H_0$	BD SOL+NPH	5-29-65	25	6/6	B	
	L	--	--	--			6/6	$N_2F_0H_0$				6/6	B	
49. Hi	R	51	F	K	33	48	6/6	B	Lente	5-31-68	24	6/6	B	
	L	--	--	--			6/6	B				6/9	B	
50. Ho	R	43	M	K	17	42	6/6	$N_1F_0H_0$	BD SOL+NPH	10-28-67	18	6/6	$N_1F_1H_0$	
	L	--	--	--			CF	$N_1F_2H_0$				HM	$N_1F_2H_1$	
51. Ka	R	61	M	K	32	48	6/12	B	BD SOL+NPH	2- 3-68	26	6/24	B	Amputation.
	L	--	--	--			6/12	B				6/18	B	
52. Kin	R	--	F	K	11	24	------	B	SOL+PZI/SOL	5-18-68	54	------	B	
	L	--	--	--			------	$N_0F_1H_0$				------	$N_0F_1H_0$	
53. Kir	R	69	F	K	62	67	6/18	B	Diet	5-10-68	26	6/9	B	
	L	--	--	--			6/24	B				6/9	B	

54. Kl	R L	54 --	M --	K --	43	50	6/36 6/18	B B	CP. 250 Phenformin	4-26-68	35	6/9 6/9	B B	
55. Kw	R L	58 --	F --	K --	53	53	6/9 6/9	B B	CP. 250	8- 9-68	27	6/9 6/9	$N_1F_1H_0$ $N_1F_1H_0$	
56. Le	R L	48 --	M --	K --	34	46	6/9 6/6	B B	SOL+PZI	7- 5-68	28	6/9 6/6	B B	
57. M. L	R L	60 --	F --	K --	45	57	6/5 6/6	B B	Lente	3- 1-68	26	6/5 6/6	B B	
58. S. L	R L	61 --	F --	K --	46	57	6/12 6/60	B $N_1F_0H_0$	SOL+NPH	3-30-68	38	6/12 6/36	B B	
59. Lo	R L	61 --	M --	K --	57	57	HM 6/12	F_2^+ $N_2F_1H_0$	Diet	9-15-67	13	HM 6/18	F_2^+? $N_2F_2H_0$	
60. Ly	R L	29 --	F --	N --	15	26	6/6 6/6	B B	Lente	7- 5-68	26	6/6 6/6	B B	
61. Ma	R L	68 --	F --	K --	51	60	6/12 6/24	B B	CP. 350	2-16-68	59	6/12 6/18	B B	
62. Mo	R L	69 --	F --	K --	67	67	6/5 6/6	B B	Diet	9- 8-67	10	6/6 6/6	B B	
63. Ned	R L	51 --	M --	K --	28	49	6/5 6/5	B B	PZI+SOL	1-27-68	23	6/9 6/9	B B	
64. Nel	R L	51 --	M --	N --	44	48	6/9 6/9	B B	CP. 250	1-20-68	18	6/6 6/6	B B	
65. Ni	R L	53 --	M --	K --	59	59	6/9 6/9	B B	TOLB 0.5BD	1-26-68	40	6/9 6/9	B $N_1F_0H_0$	
66. No	R L	55 --	M --	K --	24	50	6/18 6/9	$N_1F_1H_0$ $N_1F_0H_0$	BD SOL+NPH	12-15-67	29	HM 6/36	$?H_2F_2$ $N_1F_0H_1$	
67. Or	R L	47 --	M --	K --	25	42	6/6 6/6	B B	BD SOL+NPH	9-29-68	29	6/6 6/6	B B	Amputation.
68. Pa	R L	59 --	M --	K --	48	56	6/6 6/6	B B	CP 350 Phenformin	3-15-68	25	6/5 6/5	$N_1F_0H_0$ $N_1F_0H_0$	
69. Pri	R L	42 --	M --	K --	31	31	6/6 6/6	B B	BD SOL	9-15-66	22	6/6 6/6	$N_1F_0H_0$ $N_1F_0H_0$	
70. Pry	R L	64 --	M --	K --	57	61	6/9 6/5	B B	BD SOL+NPH	4-19-68	23	6/6 6/6	B B	TB.

E. M. KOHNER, T. R. FRASER, G. F. JOPLIN, AND N. W. OAKLEY—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Mode of therapy	Date of last exam	Duration of follow-up (months)	Visual acuity at last exam	Classification of retinopathy at last exam	Complications
71. Ra	R	--	M	K	10	28	6/36	$N_1F_2H_1$	BD SOL+NPH	3- 2-68	29	6/6	$N_0F_2H_0$	
	L	--	--	--			6/60	$N_0F_2H_0$				6/60	$N_0F_2H_0$	
72. Ram	R	50	M	K	30	46	6/6	$N_1F_0H_0$	BD SOL+NPH	1-27-68	26	6/36	H_2	
	L	--	--	--			6/6	$N_1F_0H_0$				6/6	$N_1F_0H_0$	
73. Ri	R	57	M	K	41	55	6/60	$N_1F_0H_0$	CP 250	5- 8-67	8	CF	$N_1F_0H_0$	Died, renal failure.
	L	--	--	--			6/18	$N_1F_0H_0$				6/60	$N_1F_0H_0$	
74. Robe	R	24	M	K	4	21	6/12	$N_2F_1H_0$	BD SOL+NPH	5-11-68	12	6/60	$N_0F_2H_0$	
	L	--	--	--			6/9	$N_0F_1H_0$				6/9	$N_1F_1H_0$	
75. Robs	R	60	F	K	40	58	6/9	B	Diet	3-15-68	57	6/6	B	
	L	--	--	--			6/12	B				6/6	B	
76. Rok	R	51	M	K	30	49	6/6	B	SOL+PZI/SOL	2- 2-68	25	6/9	$N_1F_0H_0$	
	L	--	--	--			6/9	B				6/12	B	
77. Ra	R	--	F	K	51	51	6/6	B	Diet	3-20-68	24	6/6	B	
	L	--	--	--			6/6	B				6/6	B	
78. Sc	R	59	F	K	35	49	6/36	H_2	BD Phenformin	7- 8-68	12	6/24	$N_2F_2H_1$	
	L	--	--	--			6/18	N_1F_2				6/9	$N_1F_2H_1$	
79. She	R	43	M	K	39	40	6/9	B	CP 250	1-19-68	25	6/12	$N_1F_1H_0$	Toe amputation.
	L	--					6/9	$N_1F_0H_0$				6/12	$N_1F_0H_0$	
80. Shi	R	48	F	K	44	45	6/24	$N_1F_2H_0$	BD SOL + NPH	11-9-67	12	LP	$N_1F_2H_1$	
	L	--					6/9	H_2				HM	$H_2F_2^{++}$	
81. Skelt	R	--	F	K	63	64		B	CP 250	3-18-67	12		B	
	L	--						B					B	
82. Skel	R	62	F	K	60	60	6/18	$N_1F_0H_0$	Phenformin	3- 1-68	6	6/18	$N_1F_0H_0$	
	L	--					6/5	$N_1F_0H_0$				6/5	$N_1F_0H_0$	
83. Ski	R	--	M	K	67	70	6/6	B	Diet	2-16-68	22	6/12	$N_1F_0H_0$	
	L	--					6/6	B				6/6	$N_1F_0H_0$	

84. A. S.	R L	33 --	M --	K --	4	29	6/6 6/12	$N_1F_0H_0$ $N_1F_1H_0$	BD SOL +NPH	5-29-68	21	6/5 6/24	$N_1F_1H_0$ $N_1F_1H_0$	
85. C. S.	R L	61 --	M --	K --	47	58	6/24 6/9	B B	BD SOL + NPH	4-68	27	6/36 6/9	B B	
86. H. S.	R L	41 --	M --	K --	26	36	6/12 6/9	$N_2F_1H_0$ $N_2F_1H_0$	BD SOL	2-18-67	19	CF HM	$N_2F_2H_1$ $N_2F_1H_1$	
87. J. S.	R L	54 --	F --	K --	30	50	6/6 CF	B B	BD SOL	7-6-68	16	6/5 6/36	B B	
88. St.	R L	58 --	F --	K --	50	52	6/6 6/5	$N_1F_0H_0$ $N_1F_0H_0$	CP 200	2-17-68	58	6/9 6/18	B B	
89. Sp.	R L	54 --	M --	K --	31	46	6/12 6/24	B $N_1F_0H_0$	BD SOL+NPH	5- 1-68	15	CF 6/36	$N_1F_0H_0$ $N_2F_0H_0$	
90. St.	R L	58 --	F --	K --	35	53	6/5 6/9	B B	Lente	7-21-67	19	6/6 6/12	$N_1F_0H_0$ B	Pyelitis
91. Te.	R L	65 --	M --	K --	59	63	6/6 6/6	B B	Diet	3-17-67	12	6/9 6/6	B B	Died, carcinoma. Coronary.
92. Th.	R L	57 --	F --	K --	47	55	6/9 6/18	$N_1F_0H_0$ B	?	2-17-67	21	6/24 6/60	$N_1F_0H_0$ $N_1F_0H_0$	
93. To.	R L	57 --	M --	N --	51	51	6/5 6/6	B B	CP 500 Phenformin	3-16-68	23	6/12 6/9	B B	
94. Tr	R L	33 --	M --	K --	20	28	6/5 6/5	$N_1F_0H_0$ $N_1F_1H_0$	BD SOL+NPH	1-20-68	16	6/5 6/5	$N_1F_0H_0$ $N_1F_1H_0$	
95. Wal.	R L	69 --	F	K --	50	67	6/18 6/18	B B	BD SOL+NPH	10-17-67	21	-------- --------	B B	
96. Wan.	R L	53 --	M --	C --	50	50	6/24 6/60	B	CP 250	2- 2-68	28	6/5 6/24	$N_1F_0H_0$ ----------	L. cataract.
97. Wate.	R L	52 --	M --	K --	22	48	6/5 HM	$N_2F_1H_0$ $N_0F_2H_0$	BD SOL+NPH	6-12-68	22	6/5 LP	$N_1F_1H_0$ $N_2F_2H_0$	
98. Watk.	R L	58 --	M --	K --	23	53	6/12 6/18	B B	BD SOL	3-22-68	21	6/36 6/18	B B	Amputation.
99. Wh.	R L	58 --	M --	K --	34	45	6/6 6/9	B B	BD SOL+NPH	7- 5-68	25	6/9 6/9	B $N_1F_0H_0$	
100. Wa.	R L	53 --	F --	K --	39	49	6/18 6/5	B $N_1F_0H_0$	BD SOL+NPH	2-23-68	28	6/6 6/18	$N_1F_0H_0$ B	

E. M. KOHNER, T. R. FRASER, G. F. JOPLIN, AND N. W. OAKLEY—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Mode of therapy	Date of last exam	Duration of follow-up (months)	Visual acuity at last exam	Classification of retinopathy at last exam	Complications
101. Will	R	--	M	K	12	38	6/5	$N_1F_0H_0$	BD SOL+NPH	2-24-68	18	6/5	$N_1F_0H_0$	
	L	--	--	--			6/5	$N_1F_0H_0$				6/24	$N_1F_0H_0$	
102. Wils	R	62	F	K	58	58	6/9	B	CP 500 Phenformin	1-12-68	14	6/5	$N_1F_0H_0$	
	L	--	--	--			6/12	B				6/18	$N_1F_0H_0$	
103. Wro	R	63	M	K	52	60	6/9	B	CP 250	3- 1-68	24	6/12	B	
	L	--	--	--			6/9	B				6/6	B	
104. Yo	R	53	M	K	34	49	6/24	B	BD SOL+NPH	7-20-68	26	6/18	B	
	L	--	--	--			6/12	B				6/18	B	

Appendix B

R. A. FIELD, T. BEHRENDT, N. T. ZERVAS, P. D. GORDY, AND T. D. DUANE

(DATA FROM CHAPTER 19)

[Mode of therapy—STEREOTAXIC TRANSSPHENOIDAL RADIOFREQUENCY PITUITARY COAGULATION]

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Date of last exam	Visual acuity at last exam	Classification of retinopathy at last exam	Degree of pituitary ablation (complete)	Complications
1. W. Q	R	26	M	W	3	18	20/200	$N_2F_0H_0$	2-14-67	11- 9-67	20/30	$N_2F_0H_0$	Yes	
	L	--	--	--			20/20	$N_2F_0H_0$			20/18	$N_2F_0H_0$		
2. J. B	R	25	M	W	5	24	20/40	$N_2F_1H_0$	3-16-67	3-23-67		$N_2F_1H_0$	Yes	
	L	--	--	--			HM							
3. D.B	R	21	M	W	18 months	19	HM		3-17-67	3-28-67	HM		Yes	
	L	--	--	--			20/30	$N_2F_2H_0$			20/30	$N_2F_2H_0$		
4. R. L	R	36	F	W	18	35	20/40	$N_1F_0H_0$	3-21-67	6-27-68		F_2 obscuring fundus.	Yes	
	L	--					20/40	$N_2F_0H_1$				$N_2F_0H_0$		
5. D.C	R	52	F	W	30	49	1/200		3-30-67	4- 5-67	HM		No criteria	
	L	--	--	--			20/200	$N_2F_1H_0$			20/200	$N_2F_1H_0$		
6. C. A	R	43	F	W	27	35	20/40	$N_2F_0H_0$	4-14-67	7-18-68	3/200	$N_2F_2H_0$ detached retina.	Yes	
	L	--	--	--			LP	$N_2F_2H_1$ detached retina.			HM	$N_2F_2H_0$ detached retina		
7. S. G	R	41	F	W	21	41	20/20	$N_1F_0H_0$	5-20-67	6- 6-67	20/40	$N_1F_0H_0$	Yes	Died 3-10-68.
	L	--	--	--			20/200	$N_1F_0H_1$			20/50	$N_1F_0H_0$		
8. C. H	R	31	M	W	12	30	20/60	$N_2F_2H_1$	5-29-67	6- 5-67	20/50	$N_2F_2H_1$	Yes	
	L	--	--	--			20/30	$N_1F_2H_1$			20/50	$N_2F_2H_1$		

R. A. FIELD, T. BEHRENDT, N. T. ZERVAS, P. D. GORDY, AND T. D. DUANE—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Date of last exam	Visual acuity at last exam	Classification of retinopathy at last exam	Degree of pituitary ablation (complete)	Complications
9. H. S.	R	35	M	W	12	34	20/26	$N_2F_0H_0$	6-19-67	6-30-67	20/20	$N_2F_0H_0$	Yes	
	L	--	--	--			20/20	$N_2F_0H_0$			20/20	$N_2F_0H_0$		
10. H. S.	R	29	M	W	6	28	HM	F_2 obscuring fundus.	8-18-67	8-25-67		F_2 obscuring fundus.	Yes	
	L	--	--	--			20/60	F_2H_2			20/30	F_2H_2		
11. M. W.	R	49	F	W	27	49	20/70	$N_2F_2H_0$	8-30-67	7-25-68	20/60	$N_2F_2H_0$	Yes	
	L	--	--	--			20/40	$N_2F_0H_0$			20/20	$N_2F_2H_0$		
12. J. M.	R	32	M	W	15	32	20/70	$N_2F_2H_1$	9-25-67	10- 7-67	20/70	$N_2F_2H_1$	Yes	
	L	--	--	--			20/40	$N_2F_1H_0$			20/40	$N_2F_1H_0$		
13. N. J.	R	26	F	W	12	22	20/70	$N_2F_0H_0$	10-13-67	3-21-68	20/80	$N_2F_0H_0$	Yes	CSF fistula due to loss of plug from sella turcica.
	L	--	--	--			20/200	$N_2F_0H_0$			20/200	$N_2F_0H_0$		
14. P. P.	R	35	F	W	14	32	20/50	H_2	10-17-67	10-27-67	20/50	H_2	Yes	
	L	--	--	--			20/40	$N_1F_0H_1$			20/40	$N_1F_0H_0$		
15. J. M.	R	28	M	W	7	27	20/400	$N_2F_2H_1$	10-23-67	7-18-68	20/400	$N_2F_2H_0$	Yes	
	L	--	--	--			20/15	$N_1F_0H_0$			20/15	$N_2F_0H_0$		
16. M. A.	R	62	F	W	32	60	20/25	$N_2F_0H_0$	10-25-67	2- 8-68	20/20	$N_2F_0H_0$	Yes	
	L	--	--	--			20/60	$N_2F_0H_0$			20/60	$N_2F_0H_0$		
17. M. R.	R	44	F	W	26	39	HM	H_2	11-20-67	7-18-68	LP		Yes	
	L	--	--	--			20/30	$N_2F_2H_1$			20/20	$N_2F_2H_1$		
18. M. W.	R	44	F	W	19	34	20/25	$N_1F_1H_0$	11-29-67	12-11-67	20/30	$N_1F_1H_0$	Yes	
	L	--	--	--			20/40	F_2 retinal detachment.			20/15	F_2 retinal detachment.		
19. R. H.	R	29	M	W	?	28	HM	H_2	12- 4-67	12-15-67		H_2	Yes	
	L	--	--	--			20/25	$N_1F_1H_1$				$N_1F_1H_1$		
20. S. C.	R	49	M	N	33	32	20/60	$N_2F_2H_0$	1-29-68	1-18-68	20/200	$N_2F_2H_0$	Yes	
	L	--	--	--			20/200	$N_2F_2H_0$			LP			

21. F. H.	R L	37 --	M --	W --	13	32	20/20 20/30	$N_2F_2H_0$ $N_1F_0H_0$ chorioretinitis.	2- 5-68	2-13-68	20/40 20/30	$N_2F_2H_0$ $N_1F_0H_0$ chorioretinitis.	Yes	OS Rx'd by photocoagulation in 1964.
22. T. C.	R L	25 --	F --	W --	9	23	20/400 20/40	F_2 obscuring fundus. $N_2F_2H_1$	2- 8-68	2-21-68	20/400 20/40	F_2 obscuring fundus.	Yes	
23. R. P.	R L	59 --	F --	W --	38	57	20/200 20/30	$N_2F_2H_0$ $N_2F_2H_1$	2-16-68	2-26-68	20/1200 20/80	$N_2F_2H_1$ $N_2F_2H_0$	Yes	
24. A. W.	R L	29 --	M --	W --	9	26	20/80 20/50	H_2 $N_1F_0H_0$	3-12-68	3-21-68	--- ---	$N_2F_0H_1$ $N_1F_0H_1$	Yes	
25. H. S.	R L	50 --	M --	W --	28	47	20/30 20/20	$N_2F_0H_0$ $N_2F_1H_0$	3-22-68	---	---	---	Yes	
26. E. M.	R L	46 --	F --	W --	26	44	20/50 20/50	F_2H_2 F_2H_2	4-23-68	4-26-68	---	F_2H_2 F_2H_2	Yes	
27. H. G.	R L	40 --	M --	W --	21	29	20/60 20/1200	--- $N_2F_0H_0$	5- 7-68	5-16-68	--- ---	--- $N_2F_0H_0$	Yes	
28. L. D.	R L	53 --	F --	W --	23	48	20/400 20/400	--- H_2	5-20-68	5-31-68	HM 20/400	--- H_2	Yes	
29. J. M.	R L	37 --	M --	W --	9	36	20/25 CF	$N_1F_0H_0$ $N_2F_2H_0$ retinal detachment.	6- 5-68	---	---	---	Yes	
30. J. L.	R L	24 --	M --	W --	14	23	20/25 20/25	$N_2F_0H_1$ $N_2F_0H_0$	7- 9-68	7-18-68	20/25 20/25	$N_2F_0H_1$ $N_2F_0H_0$	Yes	
31. L. G.	R L	24 --	F --	W --	7	23	20/30 CF	$N_2F_1H_0$ F_2H_2	7-16-68	7-25-68	20/70 HM	$N_2F_0H_0$	Yes	
32. K. R.	R L	53 --	M --	W --	29	47	20/40 20/40	F_2 obscuring fundus. $N_2F_2H_1$	7-17-68	7-25-68	20/25 20/40	F_2 obscuring fundus. $N_2F_2H_1$	Yes	
33. J. D.	R L	23 --	F --	W --	8	22	20/30 20/40	$N_2F_2H_1$ $N_2F_0H_0$	7-18-68	7-25-68	LP 20/25	--- $N_2F_0H_0$	Yes	
34. M. K.	R L	31 --	F --	W --	4	30	20/1200 20/20	$N_1F_2H_1$ retinal detachment. $N_1F_1H_1$	7-22-68	8- 1-68	--- ---	$N_1F_2H_1$ retinal detachment. $N_1F_1H_1$	Yes	
35. D. K.	R L	31 --	M --	W --	17	30	20/20 HM	$N_2F_0H_0$	7-27-68	8- 6-68	20/20 HM	$N_2F_0H_0$	Yes	

R. A. FIELD, T. BEHRENDT, N. T. ZERVAS, P. D. GORDY, AND T. D. DUANE—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Date of last exam	Visual acuity at last exam	Classification of retinopathy at last exam	Degree of pituitary ablation (complete)	Complications
36. R.R	R	45	M	W	25	44		$N_1F_1H_1$	7-28-68	8- 6-68	20/400	$N_1F_1H_0$	Yes	
	L	--	--	--							20/25	$N_2F_0H_0$		
37. R. W	R	46	F	W	26	43	20/40	$N_1F_1H_1$	12-14-66	12-14-67	20/25	$N_1F_1H_1$	Yes	
	L	--	--	--			20/1200	H_2			20/400	H_2		
38. A. R	R	49	M	W	29	48	20/30	$N_2F_1H_1$	12-15-66	6-11-68	HM	F_2H_2 retinal detachment.	Yes	
	L	--	--	--			20/1200	$N_2F_2H_1$			HM	F_2H_2 retinal detachment.		
39. P. M	R	27	M	W	7	26	20/30	$N_1F_0H_0$	1-12-67	9-14-67	20/60	$N_1F_0H_0$	No criteria	Died 10-23-67.
	L	--	--	--			20/200	$N_2F_1H_0$			20/80	$N_2F_1H_0$		
40. O. G	R	25	M	W	11	24	20/50	$N_2F_0H_0$	1-17-67				No criteria	
	L	--	--	--			HM							
41. R. G	R	45	M	W	29	43	LP		1-18-67	2- 8-68			No criteria	
	L	--	--	--			20/30	$N_2F_0H_1$				$N_2F_0H_1$		
42. M. R	R	38	F	W	21	18	20/20	$N_2F_0H_0$	2- 7-67	2-13-67		$N_2F_0H_0$	Yes	CSF Fistula due to loss of plug from sella turcica.
	L	--	--	--			20/20	$N_2F_0H_0$				$N_2F_0H_1$		

Appendix C–1

E. J. GREENBERG, B. S. RAY, A. G. PAZIANOS, W. L. PERETZ, M. ISAACS, AND B. J. KOREN

(DATA FROM CHAPTER 21)

Number and patient	Sex	Age	Date of hypophysectomy	Visual acuity				Result	Status
				Before		After			
				RE	LE	RE	LE		
1. E. E	F	30	10–24–56	20/20	HM			Unevaluated	Postoperative death at 3 weeks; coma and pneumonia.
2. R. P	M	51	10–27–56	5/200	LP	8/200	LP	Improved	Unknown.
3. A. F	F	34	3–14–57	LP	20/30	LP	20/20	do	Alive and working.
4. N. B	M	59	4–17–57	HM	8/200	NLP	CF	Unimproved	Unknown.
5. R. T	M	37	8–22–57	10/200	20/40	20/30	20/20	Improved	Died; complications of diabetic enteropathy.
6. E. H	M	25	3– 7–58	LP	20/50	15/200	20/20	do	Alive and working.
7. W. C	M	24	4–13–58	CF	20/40	20/80	20/30	do	Died; 3½ years; coronary occlusion.
8. K. G	F	33	6–26–58	LP	9/200	NLP	HM	Unimproved	Died; coronary heart disease.
9. A. L	M	54	8–27–58	LP	20/80			Unevaluated	Postoperative death at 2 days; coronary occlusion.
10. E. D	M	30	3–17–59	20/100	NLP	20/30	NLP	Improved	Died; coronary occlusion.
11. C. B	F	52	5–18–59	20/50	20/50	20/30	20/200	RE improved	Died; coronary heart disease.
12. M. T	F	54	8– 7–59	20/100	LP	LP		Unimproved	Died; gastrointestinal hemorrhage, 3 years.
13. P. W	M	55	8–19–59	CF	CF			Unevaluated	Died of serum hepatitis 4 months after surgery.
14. N. K	M	45	12–30–59	20/20	LP	20/15	LP	Improved	Alive and working.
15. E. T	M	44	4–25–60	CF	20/20			Unevaluated	Postoperative death.

E. J. GREENBERG, B. S. RAY, A. G. PAZIANO, W. L. PERETZ, M. ISAACS, AND B. J. KOREN—Continued

Number and patient	Sex	Age	Date of hypophysectomy	Visual acuity				Result	Status
				Before		After			
				RE	LE	RE	LE		
16. R. W	M	44	6–17–60	20/50	20/30			Unevaluated	Death at 6 months; coronary occlusion.
17. D. S	M	27	12– 8–60	anophthalmos	20/20	anophthalmos	20/15	Improved	Living, working, 71 months.
18. J. M	M	31	4– 6–61	20/40	LP			Unevaluated	Postoperative death.
19. D. P	M	38	8–28–61	LP	20/20	HM	20/20	Improved	Living, well, 62 months.
20. B. A	F	23	2– 6–62	3/200	HM	20/30	3/200	do	Living, working, 57 months.
21. F. R	M	37	4– 3–62	20/20	20/30	20/15	20/20	do	Death at 27 months, coronary occlusion.
22. P. K	M	29	4– 5–62	5/200	18/200	20/200	20/40	do	Death at 4 years; coronary occlusion.
23. M. F	F	40	4–17–62	20/50	HM	HM	LP	Unimproved	Living, well, 56 months.
24. S. L	M	28	1–22–63	HM	20/20	20/70	20/20	Improved	Living, working, 45 months.
25. G. S	F	34	1–23–63	20/50	5/200	20/25	20/100	do	Living, well, 45 months.
26. W. H	M	28	2–12–63	20/200	20/30	20/70	20/20	do	Living, working, 45 months.
27. V. H	F	29	2–28–63	20/15	CF	20/15	20/25	do	Living, working, 44 months.
28. V. D	F	35	4–18–63	LP	20/80	LP	20/40	Arrested	Living, well, 42 months.
29. A. D. M	M	20	4–30–63	20/70	20/200	20/20	20/70	Improved	Living, working, 42 months.
30. J. G	M	27	9–12–63	HM	HM	LP	HM	Unimproved	Living, working, 38 months.
31. H. N	M	39	9–19–63	LP	15/200	LP	NLP	do	Living, working, 37 months.
32. L. B	M	37	10– 9–63	LP	20/300	LP	LP	do	Living, well, 37 months.
33. M. K	M	36	11– 5–63	HM	20/200	20/200	20/200	Arrested	Living, well, 36 months.
34. S. M. K	F	32	1–20–64	CF	20/50	3/200	20/30	Improved	Living, working, 33 months.

35. S. M	M	24	2-20-64	CF	20/50	20/200	20/30	do	Living, working, 32 months
36. A. S.	F	28	5-19-64	LP	20/30	HM	20/30	Arrested	Living, well, 29 months.
37. D. M	M	25	6- 9-64	20/40	20/20	20/30	20/20	Improved	Living, working, 29 months.
38. W. C	M	44	6- 9-64	20/40	CF			Unevaluated	Do.
39. P. P	M	42	6-24-64	LP	20/20	LP	HM	Unimproved	Living, working, 28 months.
40. J. D	M	20	10-28-64	20/200	20/100	20/30	20/40	Improved	Living, 24 months.
41. F. R	M	29	10-29-64	4/200	20/70	HM	20/50	Arrested	Living, well, 24 months.
42. L. T	F	18	11-11-64	HM	20/70			Unevaluated	Death at 6 months; cause unknown.
43. L.S	M	19	3-15-65	20/30	20/70	20/20	20/20	Improved	Living, student, 20 months.
44. D. B	M	28	3-31-65	20/50	CF	20/40	20/200	do	Living, well, 19 months.
45. G. L. B	M	43	5-12-65	20/60	20/50	20/200	10/200	Unimproved	Living, working, 18 months.
46. G. G	F	37	6-14-65	20/70	20/40	20/200	20/30	Improved	Living, well, 17 months.
47. B. F	M	43	8-16-65	20/20	20/20	20/20	20/20	do	Living, working, 15 months.
48. C. S	F	43	11- 3-65	LP	20/40	NLP	20/40	Arrested	Living, well, 12 months.
49. J. H	M	47	11-11-65	20/40	20/200			Unevaluated	Death at 6 weeks, CVA.
50. L. B	M	27	11-23-65	20/30	20/40	20/30	20/30	Improved	Living, working, 11 months.
51. W. R	M	31	12-14-65	10/200	20/200	20/800	20/600	Unimproved	Do.
52. C. R	M	37	1-19-66	20/30	20/300	20/30	20/40	Improved	Living, working, 10 months.
53. J. C	M	39	1-21-66	20/100	20/20	20/60	20/20	Arrested	Living, well, 9 months.
54. L. B	M	41	2-11-66	4/300	10/200	20/300	20/30	Improved	Living, working, 9 months.
55. D. N	F	38	2-11-66	20/70	20/20	20/25	20/20	do	Do.
56. F. H	M	38	6- 3-66	20/200	20/40	20/60	20/40	Improved	Living, well, 5 months.

CF=Count fingers. HM=Hand motion. LP=Light perception. NLP=No light perception.

Appendix C–2

E. J. GREENBERG, B. S. RAY, A. G. PAZIANOS, W. L. PERETZ, M. ISAACS, AND B. J. KOREN

Number and patient	Sex	Age	Date of implant Y^{90}	Visual acuity				Result	Complications	Status
				Before		After				
				RE	LE	RE	LE			
1. D. F.	M	25	10–24–63	20/30	LP	20/20	NLP	Improved	CSF rhinorrhea, meningitis	Death at 13 months; renal failure.
2. N. R.	M	59	12–12–63	20/40	NLP	.....	.....	Unevaluated	Meningitis, optic nerve	Death at 2 months; coronary occlusion.
3. G. K.	M	49	1–9–64	20/200	20/100	20/200	20/70	Arrested	CSF rhinorrhea, meningitis, 6th nerve palsy.	Living, working.
4. T. V.	M	31	1–16–64	20/25	NLP	.....	.....	Unevaluated; lost to follow-up.	None known	Living.
5. G. B.	M	53	1–21–64	20/200	HM	20/70	5/200	Arrested	None	Living, working.
6. R. W.	F	53	3–25–64	5/200	12/200	10/200	15/200	do	3d nerve palsy, bitemporal field defect.	Living.
7. A. S.	F	53	4–9–64	20/80	HM	5/200	LP	Unimproved	None	Do.
8. T. P.	F	53	4–23–64	20/100	CF	20/40	20/200	Improved	CSF rhinorrhea	Do.
9. A. D.	F	31	4–30–64	15/200	20/70	20/30	20/70	do	None	Living, working.
10. T. F.	M	32	4–30–64	20/30	HM	20/20	HM	Unimproved	CSF rhinorrhea	Do.
11. V. B.	M	43	5–14–64	HM	CF	HM	8/200	Arrested	None	Living.
12. O. L.	M	53	7–2–64	20/200	20/25	.....	.....	Unevaluated	CFS rhinorrhea, meningitis aspergillosis.	Death at 5 months; CVA.
13. F. D.	M	40	8–7–64	NLP	HM	NLP	LP	Unimproved	CSF rhinorrhea, meningitis	Living.
14. H. W.	M	61	9–17–64	20/60	20/200	20/40	20/70	Improved	None	Living, working.

15. W. F	M	48	4- 2-65	20/50	20/80	20/40	20/70	Arrested	CSF rhinorrhea, meningitis; 3d, 6th nerve palsies.	Death at 11 months; massive epistaxis.
16. B. B	M	48	6- 3-65	20/50	20/80	20/40	20/70	Arrested	None	Living, working.
17. J. D	M	51	6-10-65	20/70	20/30	20/200	20/70	Unimproved	do	Living.
18. L. O	M	57	7-29-65	20/200	20/200			Incomplete	Meningitis	Do.
19. S. B	F	69	8- 5-65	20/200	20/200	20/200	20/200	Arrested	None	Death at 5 months; CVA.
20. A. D	M	58	9-30-65	5/200	20/300			Unevaluated	CSF rhinorrhea, meningitis, hemorrhage.	Death at 7 weeks.
21. I. S	F	43	10-21-65	20/40	20/60	20/25	20/60	Improved	None	Living, working.
22. J. W	M	55	4-13-66	HM	20/40			Unevaluated	CSF rhinorrhea, pneumoencephalos, meningitis.	Death at 10 weeks.

CF=Count fingers. HM=Hand motion. LP=Light perception. NLP=No light perception.

Appendix D

J. HARDY, A. PANISSET, A. MARCHILDON, AND A. LANTHIER

(DATA FROM CHAPTER 22)

(Mode of therapy—TRANSSPHENOIDAL HYPOPHYSECTOMY)

Patient and Number	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy (TS. HX.)	Date of last exam	Duration of follow-up (months)	Visual acuity at last exam	Visual retention index *	Classification of retinopathy at last exam	Degree of pituit. ablation	Complications
1. M. D.	R	61	F	W	49	58	LP	$BH_1N_2F_2$	11- 1-65		7- 4-68	28	HM		$BH_0N_2F_2$		DI
	L	--	--	--			20/200	$BH_0N_2F_1$		Total			HM	0.8	$BH_0N_2F_2$	C	
2. P. S.	R	33	M	W	12		20/30	$BH_0N_2F_1$	3- 3-66		12-20-67	15	20/20	1	$BH_0N_0F_1$		
	L	--	--	--			20/30	$BH_0N_2F_2$		Total			20/20	1	$BH_0N_0F_2$	C	
3. A. C.	R	59	M	W	57	57	20/400	$BH_0N_1F_0$	4-12-66		3-26-68	24	HM	0.6	BH_2		transient CSFR
	L	--	--	--			LP	$BH_0N_1F_0$		Total			CF		$BH_1N_2F_2$	C	
4. A. D.	R	25	M	W	9	24	20/400	$BH_0N_2F_2$	4-13-66		3-11-68	23	LP	0.5	BH_2		
	L	--	--	--			20/400	$BH_0N_2F_2$		Total			20/200	1	$BH_0N_2F_2$	C	
5. L. G.	R	56	M	W	50	52	20/40	$BH_0N_0F_0$	4-26-66		3-14-68	23	20/30	1	$BH_0N_0F_0$		
	L	--	--	--			20/70	$BH_1N_0F_0$		S. Ant			5/400	0.04	BH_2	C	
6. R. L.	R	45	M	W	42	43	LP	BH_2	4-26-66		6-17-68	25	20/400	1	$BH_1N_2F_2$		
	L	--	--	--			20/200	$BH_0N_0F_0$		Total			20/80	1	$BH_0N_0F_0$	C	
7. G. M.	R	45	F	W	25	42	20/80	$BH_0N_1F_0$	5-26-66		4-24-68	22	20/60	1	$BH_0N_0F_0$		
	L	--	--	--			20/800	$BH_0N_2F_0$		S. Ant			20/800	1	$BH_0N_0F_1$	C	
8. J. M.	R	28	F	W	5	24		$BH_0N_2F_2$	9-21-66		6-28-67	8	CF		$BH_0N_2F_2$		
	L	--	--	--				$BH_0N_2F_2$		S. Ant			20/300	1	$BH_0N_2F_2$	C	
9. M. G.	R	29	F	W	15	27	20/400	$BH_0N_0F_0$	6-14-66		1- 5-67	7	20/40	1	$BH_0N_0F_0$		
	L	--	--	--			20/200	$BH_0N_0F_0$		S. Ant			20/20	1	$BH_0N_0F_0$	C	

10. T. R.	R	24	F	W	12	22		$BH_0N_2F_0$	10-20-66		3-15-68	17	20/30	1	normal		DI
	L	--	--	--				$BH_0N_0F_0$		S. Ant.			20/20	1	normal	C	
11. B. P.	R	29	M	W	11	26	20/400	$BH_0N_2F_0$	12-22-66		1-12-68	13	20/200	1	$BH_0N_0F_0$		DI
	L	--	--	--			20/25	$BH_0N_1F_0$		S. Ant.			20/40	0.6	$BH_0N_1F_0$	C	
12. F. G.	R	34	M	W	8	31	20/60	$BH_0N_2F_2$	1-16-67		3-25-68	15	20/200	0	$BH_0N_2F_2$		DI
	L	--	--	--			LP	$BH_0N_2F_2$		S. Ant.			LP		$BH_1N_2F_2$	C	
13. L. G.	R	54	F	W	35	34	10/400	$BH_1N_2F_2$	1-31-67		9-30-67	8	20/400	1	$BH_0N_2F_2$		
	L	--	--	--			20/60	$BH_0N_2F_0$		S. Ant.			20/400	0.3	$BH_0N_2F_2$	C	
14. R. D.	R	31	M	W	28	29	20/20	$BH_0N_1F_0$	1-31-67		11- 8-67	10	20/20	1	$BH_0N_0F_0$		DI
	L	--	--	--			20/20	$BH_0N_1F_0$		S. Ant.			20/20	1	Normal	C	
15. J. M.	R	24	M	W	11	23	20/30	$BH_0N_1F_0$	2- 9-67		4- 2-68	14	20/25	1	$BH_0N_1F_0$		DI
	L	--	--	--			20/30	$BH_0N_1F_0$		S. Ant.			20/20	1	$BH_0N_1F_0$	C	
16. G. L.	R	29	M	W	10	29	5/400	$BH_0N_0F_0$	3- 7-67		7 12-67	5	LP	0.5	BH_2		
	L	--	--	--			20/400	BH_2		Total			HM	0.75	BH_2	C	
17. R. B.	R	35	F	W	32	33	20/200	$BH_0N_1F_0$	5-12-67		3-11-68	10	20/50	1	$BH_0N_0F_0$		
	L	--	--	--			20/600	$BH_0N_0F_0$		S. Ant.			CF	0.3	BH_2	C	
18. M. V.	R	46	M	W	44	45	10/100	$BH_0N_2F_1$	7- 6-67		3- 8-68	8	20/200	0.2	$BH_0N_2F_1$		
	L	--	--	--			20/60	$BH_0N_2F_1$		Total			20/200	0.2	$BH_0N_2F_1$	C	
19. J. N.	R	32	M	W	16	31	LP	BH_2	8-17-67		3- 7-68	7	20/200	1	$BH_0N_2F_2$		
	L	--	--	--			20/40	$BH_0N_2F_2$		Total			20/20	1	$BH_0N_2F_2$	C	
20. R. B.	R	46	M	W	41	45	HM	$BH_0N_0F_0$	9-11-67								DI
	L	--	--	--			HM	$BH_0N_0F_0$		S. Ant.						C	
21. J. F.	R	55	F	W	34	48	LP	BH_2	9-11-67		4-24-68	7	LP		BH_2		
	L	--	--	--			20/70	$BH_0N_0F_0$		S. Ant.			20/40	1	$BH_0N_0F_0$	C	
22. M. D.	R	58	F	W	38	53	20/200	$BH_0N_1F_0$	12-12-67		4- 5-68	4	20/200	1	$BH_0N_1F_0$		
	L	--	--	--			20/50	$BH_0N_1F_0$		Total			20/50	1	$BH_0N_1F_0$	C	
23. C. T.	R	53	F	W	51	52	20/200	$BH_0N_0F_0$	12-14-67		2- 6-68	2	20/50	1	$BH_1N_0F_0$		
	L	--	--	--			20/40	$BH_0N_0F_0$		S. Ant.			20/40	1	$BH_1N_2F_0$	C	
24. R. L.	R	40	M	W	20	37	20/30	$BH_0N_2F_2$	12-21-67		7-15-68	7	20/70	0.5	$BH_1N_2F_2$		
	L	--	--	--			LP	BH_2		Total			20/30	1	$BH_1N_2F_2$	C	
25. R. L.	R	34	M	W	9	32	20/50	$BH_1N_2F_0$	1- 4-68		3-28-68	3	20/400	0	$BH_1N_2F_1$		
	L	--	--	--			20/70	$BH_0N_0F_0$		S. Ant.			20/60	0.3	$BH_0N_0F_0$	C	

See footnote at end of table.

J. HARDY, A. PANISSET, A. MARCHILDON, AND A. LANTHIER—Continued

Patient and Number	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy (TS. HX.)	Date of last exam	Duration of follow-up (months)	Visual acuity at last exam	Visual retention index *	Classification of retinopathy at last exam	Degree of pituit. ablation	Complications
26. P. G.	R	50	F	W	35	50	20/100	$BH_1N_0F_0$	1- 4-68		5- 9-68	4	20/20	1	$BH_0N_0F_0$		
	L	--	--	--			20/25	$BH_0N_0F_0$		Total			20/25	1	$BH_0N_0F_0$	C	
27. A. D.	R	59	F	W	42	56	20/30	$BH_0N_2F_0$	1-23-68		8-20-68	7	20/200	0.5	$BH_0N_1F_2$		
	L	--	--	--			LP	$BH_1N_2F_0$		S. Ant			LP		$BH_1N_2F_1$	C	
28. S. D.	R	49	F	W	49	49	20/20	$BH_0N_0F_0$	1-24-68		7- 4-68	6	20/20	1	$BH_0N_0F_0$		
	L	--	--	--			20/20	$BH_0N_0F_0$		S. Ant			20/20	1	$BH_0N_0F_0$	C	
29. A. T.	R	53	M	W	36	51	20/200	$BH_0N_0F_0$	2- 2-68		6-22-68	4	20/400	0.5	$BH_0N_0F_0$		
	L	--	--	--			CF	$BH_0N_2F_2$		S. Ant			CF		$BH_0N_2F_2$	C	
30. F. M.	R	38	M	W	28	28	20/50	$BH_0N_2F_0$	2-23-68		7- 8-68	5	20/200	0.8	$BH_1N_2F_0$		DI
	L	--	--	--			20/40	$BH_0N_2F_1$		S. Ant			LP	0.4	BH_2	C	

*visual retention index = $\frac{\text{\# mos. vision sustained}}{\text{\# mos. patient followed}}$

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Appendix E

R. N. KJELLBERG, J. W. McMEEL, V. McMANUS, AND A. M. KOEHLER

(DATA FROM CHAPTER 23)

[Mode of therapy—BRAGG PEAK PROTON BEAM HYPOPHYSECTOMY]

Patient No.	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Date of last exam	Duration of followup (months)	Visual acuity at last exam	Visual retention index *	Classification of retinopathy at last exam	Degree of pituitary ablation
1.	R	30	F	W	10	29	CF	$N_1F_1H_1$	5-62	9-62	4	CF	3/4	$N_1F_0H_1$	Partial.
	L	--	--	--			CF	H_1				CF	3/4	H_1	
2.	R	30	F	W	10	29	20/70	$N_1F_1H_1$	10-62	11-66	49	20/40	36/36	$N_1F_2H_1$	Complete.
	L	--	--	--			20/200	F_2H_1				20/40	36/36	$N_1F_1H_0$	
3.	R	36	M	W	15	35	LP	H_2	10-62	10-63	12		0/12		Complete.
	L	--	--	--			20/70	$N_2F_2H_0$					0/12		
4.	R	58	F	W	31	54	Proj		10-62	10-66	48	Proj			Complete.
	L	--	--	--			20/200					HM	4/40	F_2H_2	
5.	R	54	F	W	34	32	20/50	$N_2F_2H_0$	10-62	12-66	50	20/100	0/37	N_1F_2	Partial.
	L	--	--	--			CF	N_0F_0				CF	37/37	$N_1F_2H_1$	
6.	R	43	F	W	18	28	20/70		12-62	12-66	48	20/70	48/48	$N_1F_2H_1$	Complete.
	L	--	--	--			HM					HM	48/48	H_2	
7.	R	57	M	W	50	48	HM		12-62	10-66	46	LP	46/46		Complete.
	L	--	--	--			20/70	$N_1F_1H_1$				HM	3/46	H_2	
8.	R	38	M	W	11	33	20/40	$N_1F_1H_1$	12-62	9-65	33	LP	16/33	H_1	Complete.
	L	--	--	--			LP					NLP	0/33		
9.	R	61	F	W	39	59	HM	H_2	12-62	6-66	42	NLP	0/42		
	L	--	--	--			20/100	H_1				HM	7/42		
10.	R	39	M	W	16	36	20/200	$N_1F_1H_1$	1-63	1-64	12	CF	0/6		Complete.
	L	--	--	--			20/25	$N_1F_0H_0$				20/20	6/6		
11.	R	49	F	W	39	31	20/200	$N_2F_2H_1$	1-63	10-67	57	HM	10/57		Complete.
	L	--	--	--			20/25	$N_1F_2H_0$				20/70	50/57	$N_1F_2H_1$	

See footnote at end of table.

R. N. KJELLBERG, J. W. McMEEL, V. McMANUS, AND A. M. KOEHLER—Continued

Patient No.	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Date of last exam	Duration of followup (months)	Visual acuity at last exam	Visual retention index *	Classification of retinopathy at last exam	Degree of pituitary ablation
12.	R	32	M	W	5	30	20/50	$N_1F_1H_1$	1–63	7–63	6	NLP	1/6	$N_1F_1H_1$	Complete.
	L	--	--	--			LP					NLP	4/6		
13.	R	62	F	W	41	39	20/70	$N_2F_2H_0$	2–63	11–63	9	HM	0/9	H_2	N.A.
	L	--	--	--			HM	$N_2F_2H_1$				HM	1/9	H_2	
14.	R	58	M	W	55	56	20/30	$N_2F_0H_0$	2–63	3–67	49	20/50	47/48	$N_2F_2H_1$	Complete.
	L	--	--	--			20/30	$N_2F_0H_0$				HM	47/48	H_2	
15.	R	51	M	W	40	49	20/100	$N_1F_1H_1$	2–63	8–64	18	20/100	13/13	$N_1F_2H_1$	Complete.
	L	--	--	--			CF	H_2				20/200	13/13	$N_1F_2H_1$	
16.	R	52	M	W	16	49	20/100	$N_1F_2H_1$	2–63	8–66	42	LP	25/42		Complete.
	L	--	--	--			20/200	F_2H_1				LP	0/42		
17.	R	74	F	W	63	62	20/100	$N_1F_0H_0$	2–63	1–68	59	20/100	18/18	$N_1F_0H_0$	Complete.
	L	--	--	--			HM	$N_1F_0H_0$				CF	18/18	$N_1F_0H_0$	
18.	R	64	M	W	8	62	20/70	$N_1F_1H_1$	3–63	6–66	39	20/70	30/30	$N_1F_1H_1$	Complete.
	L	--	--	--			NLP					NLP			
19.	R	27	F	W	13	26	CF	$N_2F_2H_0$	3–63	12–63	9				Complete.
	L	--	--	--			HM	$N_2F_2H_1$							
20.	R	28	M	W	13	26	20/25	$N_1F_0H_0$	3–63	12–67	57	HM	31/56	H_2	Complete.
	L	--	--	--			20/30	H_1				20/60	41/56	$N_1F_2H_1$	
21.	R	61	F	W	27	55	20/50	$N_1F_0H_1$	3–63	9–66	42	NLP	23/36		Complete.
	L	--	--	--			LP					LP	36/36		
22.	R	49	M	W	26	46	HM	$N_1F_1H_1$	3–63	3–65	24	NLP	0/18	H_1	Complete.
	L	--	--	--			HM	$N_2F_2H_1$				NLP	0/18	F_2H_2	
23.	R	66	F	W	53	63	20/300	$N_1F_1H_0$	5–63	11–67	54	HM	36/53	$N_1F_1H_1$	Partial.
	L	--	--	--			CF	$N_1F_2H_1$				HM	53/53	$N_1F_2H_1$	
24.	R	69	M	W	48	68	20/70	$N_1F_0H_1$	5–63	8–66	39	NLP	0/39		None.
	L	--	--	--			20/400	$N_1F_0H_1$				NLP	0/39		

25.	R	28	M	W	14	27	20/200		5–63	1–68	56	NLP	3/56		Complete.
	L	--	--	--			CF					NLP	0/56		
26.	R	37	M	W	1	29	NLP		5–63	5–66	36	NLP			Complete.
	L	--	--	--			20/40	$N_2F_2H_1$				20/80	23/36	$N_2F_2H_0$	
27.	R	30	M	W	12	27	20/40	$N_2F_2H_1$	5–63	8–65	27	HM	0/27	$N_1F_2H_0$	Complete.
	L	--	--	--			CF	N_2H_1				NLP	0/27		
28.	R	68	F	W	55	62	20/100	$N_1F_1H_1$	6–63	8–66	38	LP	0/32	H_2	Partial.
	L	--	--	--			20/200	$N_1F_2H_1$				LP	0/32	H_1	
29.	R	43	M	W	30	41	Enuc		6–63	8–65	26				Complete.
	L	--	--	--			20/25	$N_1F_1H_1$				HM	16/26	$N_1F_1H_0$	
30.	R	40	M	W	23	39	HM	$N_2F_2H_2$	6–63	7–65	25	20/80	25/25	H_2	Partial.
	L	--	--	--			45/200	F_2H_1				HM	0/25	H_1	
31.	R	56	M	W	34	54	20/25	$N_2F_2H_1$	6–63	4–66	34	20/50	17/34	H_2	Complete.
	L	--	--	--			LP	H_2				LP	34/34	H_2	
32.	R	70	F	W	54	65	20/30	$N_1F_1H_1$	6–63	10–65	28	20/20	28/28	$N_1F_2H_0$	None.
	L	--	--	--			CF	N_2F_1				20/300	28/28	$N_1F_2H_0$	
33.	R	41	M	W	9	35	20/400	H_2	6–63	8–64	14	Sustained	7/14		Complete.
	L	--	--	--			20/30	$N_2F_1H_0$				do	7/14		
34.	R	29	F	W	15	25	20/70	$N_2F_2H_1$	6–63	5–66	35	20/50	33/33	$N_2F_2H_0$	Complete.
	L	--	--	--			20/50	$N_1F_2H_0$				CF	0/33	N_0F_0	
35.	R	33	F	W	13	29	20/25	$N_1F_2H_1$	6–63	9–66	39	20/30	39/39	$N_1F_2H_0$	Complete.
	L	--	--	--			HM					LP	39/39		
36.	R	38	F	W	14	37	CF		6–63	9–66	39	CF	39/39	H_1	Complete.
	L	--	--	--			20/25					20/20	39/39	H_0	
37.	R	67	F	W	61	65	CF	$N_1F_0H_0$	8–63	6–65	22	CF	19/19	$N_1F_0H_0$	Partial.
	L	--	--	--			15/200	$N_1F_0H_0$				CF	13/19	$N_1F_0H_0$	
38.	R	50	F	W	35	48	20/40	$N_2F_2H_0$	8–63	2–66	30	NLP	0/25	H_0	Partial.
	L	--	--	--			LP	$N_2F_2H_0$				HM	25/25	$N_2F_2H_1$	
39.	L	60	M	W	40	58	20/70	$N_1F_1H_1$	8–63	6–66	34	LP	2/34	$N_1F_1H_1$	Complete.
	L	--	--	--			20/200	H_2				NLP	0/34	H_2	
40.	R	63	F	W	59	56	HM		8–63	4–65	20	LP	0/20	H_2	Partial.
	L	--	--	--			20/70					CF	0/20	H_0	
41.	R	35	M	W	22	32	20/30	$N_1F_1H_0$	8–63	5–64	9	Sustained	8/8		Complete.
	L	--	--	--			CF					do	8/8		

See footnote at end of table.

R. N. KJELLBERG, J. W. McMEEL, V. McMANUS, AND A. M. KOEHLER—Continued

Patient No.	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Date of last exam	Duration of followup (months)	Visual acuity at last exam	Visual retention index *	Classification of retinopathy at last exam	Degree of pituitary ablation
42.	R	43	M	W	29	42	20/100	$N_2F_2H_1$	9–63	12–63	3	20/100	3/3	$N_2F_2H_1$	Complete.
	L	--	--	--			CF	$N_1F_2H_2$				CF	3/3	H_2	
43.	R	46	M	W	15	43	20/70		9–63	4–66	31	CF	0/31	$N_1F_2H_0$	Complete.
	L	--	--	--			CF					20/200	31/31	$N_1F_2H_0$	
44.	R	50	F	W	34	48	HM	$N_2F_2H_1$	10–63	6–66	32	LP	0/32		Complete.
	L	--	--	--			20/70	$N_2F_2H_1$				LP	0/32		
45.	R	34	M	W	17	33	LP		10–63	4–64	6	NLP	0/6		Complete.
	L	--	--	--			20/25	$N_2F_2H_1$				LP	0/6		
46.	R	44	M	W	31	41	20/200	N_1H_1	10–63	1–66	27	LP	12/15	H_1	Complete.
	L	--	--	--			20/100	F_1H_0				20/25	15/15	H_0	
47.	R	35	M	W	17	29	CF	$N_1F_2H_1$	10–63	8–67	46	CF	46/46	$N_1F_2H_1$	Complete.
	L	--	--	--			CF	$N_2F_2H_1$				HM	46/46	$N_1F_2H_0$	
48.	R	59	F	W	38	57	HM	F_2H_2	10–63	6–66	32	HM	24/24		None.
	L	--	--	--			20/70	$N_1F_2H_1$				HM	6/24	F_2H_2	
49.	R	32	F	W	14	30	20/50	$N_2F_0H_0$	12–63	8–66	32	20/200	8/32	F_2H_2	Complete.
	L	--	--	--			20/400	$N_1F_0H_0$				20/40	32/32	$N_1F_1H_0$	
50.	R	44	M	W	19	40	CF	N_1H_1	12–63	3–66	27	20/20	16/16	$N_1F_0H_0$	Complete.
	L	--	--	--			20/20	$N_1F_1H_0$				20/40	16/16	$N_1F_1H_0$	
51.	R	45	M	W	22	43	20/20	$N_2F_1H_1$	12–63	9–66	33	20/30	33/33	$N_1F_1H_1$	Complete.
	L	--	--	--			HM	H_0				NLP	0/33	H_2	
52.	R	58	F	W	34	56	20/30	$N_1F_2H_1$	12–63	8–66	32	20/200	16/32		None.
	L	--	--	--			CF	$N_2F_2H_1$				LP	0/32		
53.	R	51	M	W	41	47	HM	$N_2F_2H_1$	12–63	6–65	18	HM	9/9		Complete.
	L	--	--	--			20/400	$N_2F_2H_1$				20/400	9/9	H_1	
54.	R	40	M	W	18	37	20/50	$N_1F_1H_1$	12–63	1–66	25		0/7		Complete.
	L	--	--	--			LP	H_2				Enuc	0/7		

55.	R L	38 --	M --	W --	11	37	20/50 Enuc.	$N_2F_1H_1$	1–64	2–64	1	Enuc.			N.A.
56.	R L	52 --	M --	W --	41	51	HM 20/40	$N_2F_1H_2$ H_1	1–64	2–68	49	20/200 HM	49/49 6/49	$N_1F_1H_1$ H_2	Complete.
57.	R L	36	F	W	12	27	Enuc. 20/200	 $N_1F_2H_0$	1–64	5–68	52	Enuc. 15/200	 31/52	 $N_1F_2H_0$	Complete.
58.	R L	43	F	W	10	41	20/200 20/200	$N_2F_2H_1$ $N_1F_2H_1$	1–64	3–68	50	20/30 CF	33/33 0/33	$N_1F_2H_0$ $N_1F_2H_0$	Complete.
59.	R L	33 --	F --	W --	8	29	CF 20/40	F_2H_1 $N_2F_2H_1$	3–64	9–65	18	CF 20/40	14/14 14/14	F_2H_1 $N_2F_2H_1$	Complete.
60.	R L	39 --	M --	W --	22	38	20/400 20/60	$N_2F_1H_1$ $N_2F_1H_0$	3–64	2–67	35	HM 20/25	0/33 33/33	 	Complete.
61.	R L	44 --	M --	W --	17	35	20/200 HM	 	3–64	2–68	47	HM HM	0/38 38/38	 	Complete.
62.	R L	62 --	M --	W --	21	54	LP 20/200	 	3–64	4–64	1	 20/200	 1/1	 	N.A.
63.	R L	51 --	M --	W --	50	50	20/50 CF	$N_2F_0H_0$ $N_2F_0H_0$	3–64	12–64	9	LP HM	0/9 0/9	 	Complete.
64.	-- --	56 --	F --	W --	49	50	20/70 20/30	$N_2F_2H_1$ $N_1F_0H_0$	4–64	12–66	32	 20/20	0/32 32/32	H_1 $N_1F_0H_0$	Complete.
65.	R L	54 --	M --	W --	21	51	20/25 LP	$N_1F_2H_1$ H_2	4–64	9–65	17	CF NLP	6/17 0/17	$N_1F_2H_1$ 	Complete.
66.	R L	24 --	F --	W --	12	22	CF 20/30	$N_1F_2H_0$ $N_1F_2H_1$	4–64	11–65	19	CF 20/20	14/14 14/14	$N_1F_2H_0$ $N_1F_2H_0$	Complete.
67.	R L	47 --	M --	W --	15	33	20/40 LP	$N_1F_1H_1$ F_2H_2	4–64	2–66	22	15/200 LP	1/19 0/19	F_2H_1 	Complete.
68.	R L	48 --	F --	W --	12	44	LP 20/40	$N_2F_2H_0$ $N_1F_2H_0$	5–64	6–67	37	LP 20/40	37/37 37/37	 	Complete.
69.	R L	41 --	F --	W --	12	36	HM 20/25	 $N_2F_2H_0$	5–64	8–66	27	LP 20/25	24/24 24/24	 $N_1F_2H_0$	Complete.
70.	R L	36 --	F --	W --	10	33	20/70 HM	 	5–64	8–66	27	LP LP	0/22 10/22	 	Complete.
71.	R L	34 --	M --	W --	16	34	20/40 20/100	$N_2F_2H_0$ $N_2F_2H_1$	5–64	10–66	29	20/60 HM	10/13 0/13	$N_1F_2H_1$ 	None.

See footnote at end of table.

R. N. KJELLBERG, J. W. McMEEL, V. McMANUS, AND A. M. KOEHLER—Continued

Patient No.	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Date of last exam	Duration of followup (months)	Visual acuity at last exam	Visual retention index *	Classification of retinopathy at last exam	Degree of pituitary ablation
72.	R	61	M	W	50	48	20/40	$N_2F_1H_1$	7-64	10-66	27	20/20	21/21		Complete.
	L	--	--	--			LP								
73.	R	29	F	W	12	27	20/100	$N_2F_1H_0$	7-64	5-68	46	20/40	46/46	$N_1F_2H_0$	Partial.
	L	--	--	--			LP	N_2F_2				NLP	0/46		
74.	R	41	F	W	7	28	20/20	$N_1F_0H_0$	7-64	10-66	27	20/25	27/27	$N_1F_1H_0$	Partial.
	L	--	--	--			LP					NLP	0/27		
75.	R	46	F	W	26	41	HM	H_2	7-64	5-65	10				Complete.
	L	--	--	--			20/100	$N_1F_0H_1$							
76.	R	26	F	W	6	25	20/30	$N_2F_2H_0$	7-64	12-66	29	20/400	1/26	$N_1F_2H_1$	Partial.
	L	--	--	--			HM	$N_2F_2H_2$				HM	26/26	H_2	
77.	R	47	F	W	15	37	Enuc		7-64	2-68	43	Enuc			Complete.
	L	--	--	--			20/40	$N_1F_1H_1$				20/20	43/43	$N_1F_1H_1$	
78.	R	32	M	W	15	31	20/50	$N_1F_1H_1$	9-64	10-66	25	20/60	25/25		Partial.
	L	--	--	--			20/30	$N_1F_1H_1$				20/50	25/25		
79.	R	56	M	W	41	52	20/70	$N_1F_0H_0$	9-64	8-65	11	20/50	11/11	$N_1F_1H_0$	None.
	L	--	--	--			LP	H_2				HM	11/11	H_2	
80.	R	40	M	W	12	38	20/100	$N_2F_2H_1$	9-64	5-65	8	20/80	8/8	$N_2F_2H_1$	Partial.
	L	--	--	--			20/100	$N_1F_2H_0$				6/20	8/8	$N_1F_2H_0$	
81.	R	35	F	W	18	33	HM	H_2	9-64	6-67	33	NLP	0/33	H_1	Complete.
	L	--	--	--			20/30	$N_2F_2H_1$				20/500	11/33	$N_1F_2H_1$	
82.	R	39	F	W	13	27	20/20	$N_1F_1H_1$	11-64	11-65	12	20/20	10/10	$N_1F_1H_0$	Complete.
	L	--	--	--			20/400	F_2H_2				LP	0/10		
83.	R	53	F	W	20	51	20/25		12-64	1-67	25	20/30	24/24		Partial.
	L	--	--	--			20/70					20/30	24/24		
84.	R	52	M	W	24	46	20/25	$N_2F_0H_0$	12-64	12-66	24	CF	18/24	$N_2F_2H_1$	Complete.
	L	--	--	--			20/70	$N_2F_2H_1$				20/70	24/24	$N_1F_2H_1$	

85.	R L	49 --	M --	W --	31	30	20/40 CF	$N_1F_0H_1$ $N_1F_1H_2$	12-64	11-66	23	20/50 HM	22/22 22/22	$N_1F_0H_1$ $N_1F_1H_2$	Complete.
86.	R L	25 --	M --	W --	4	23	CF 20/40	$N_2F_2H_2$ $N_1F_2H_0$	12-64	10-65	10	HM 20/200	10/10 0/10	 $N_2F_2H_1$	Complete.
87.	R L	38 --	M --	W --	17	36	20/70 20/200	$N_1F_0H_0$ $N_1F_1H_0$	12-64	11-66	23	20/30 20/50	23/23 23/23	$N_1F_0H_0$ $N_1F_1H_0$	Complete.
88.	R L	30 --	M --	W --	5	28	HM 20/20	$N_0F_2H_1$ $N_2F_0H_0$	12-64	7-65	7	HM 20/25	7/7 7/7	... 	None.
89.	R L	37 --	F --	W --	10	33	20/40 CF	$N_1F_2H_1$ $N_2F_2H_1$	1-65	1-68	36	LP NLP	17/36 0/36	$N_1F_2H_1$ $N_2F_2H_1$	Partial.
90.	R L	47 --	F --	W --	23	45	HM 20/200	 	1-65	12-65	11	HM 20/400	11/11 11/11	$N_1F_2H_0$ $N_1F_2H_1$	Complete.
91.	R L	55 --	M --	W --	42	51	20/40 HM	$N_2F_1H_0$ H_2	1-65	6-67	29	HM HM	26/29 29/29	$N_1F_2H_0$ 	Complete.
92.	R L	49 --	F --	W --	30	47	CF 20/40	H_2 $N_2F_2H_1$	1-65	1-67	24	LP HM	0/10 0/10	 	None.
93.	R L	41 --	M --	W --	3	40	20/50 20/30	$N_2F_2H_1$ $N_1F_1H_1$	1-65	2-67	25	20/30 LP	17/17 0/17	$N_1F_2H_1$ H_2	Partial.
94.	R L	47 --	M --	W --	45	45	20/70 20/25	$N_2F_2H_1$ $N_1F_1H_0$	2-65	1-66	11	20/50 20/30	11/11 11/11	$N_2F_2H_1$ $N_1F_1H_0$	N.A.
95.	R L	23 --	F --	W --	9	22	20/40 20/200	$N_2F_1H_0$ $N_2F_1H_0$	2-65	3-66	13	HM CF	0/13 0/13	$N_2F_1H_0$ $N_2F_1H_0$	None.
96.	R L	40 --	F --	W --	11	32	20/400 HM	$N_2F_2H_1$ 	2-65	1-68	35	20/60 LP	30/30 0/30	$N_1F_2H_0$ $N_1F_2H_0$	Complete.
97.	R L	25 --	M --	W --	18	24	LP 30/20	H_2 $N_2F_1H_0$	2-65	3-67	25	LP 20/30	0/4 4/4	H_2 $N_2F_1H_0$	Complete.
98.	R L	43 --	M --	W --	17	36	20/20 CF	$N_1F_2H_0$ N_1F_2	3-65	3-67	24	20/20 CF	24/24 24/24	$N_1F_2H_0$ F_2H_0	Partial.
99.	R L	54 --	M --	W --	29	45	20/50 20/200	N_0F_0 $N_1F_2H_1$	3-65	3-67	24	20/50 20/400	24/24 24/24	N_0F_0 $N_1F_2H_0$	None.
100.	R L	54 --	F --	W --	30	30	HM 20/40	$N_1F_2H_0$ $N_2F_1H_1$	3-65	10-66	19	HM 20/40	3/3 3/3	$N_1F_2H_1$ $N_2F_1H_1$	None.

See footnote at end of table.

R. N. KJELLBERG, J. W. McMEEL, V. McMANUS, AND A. M. KOEHLER—Continued

Patient No.	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Date of last exam	Duration of followup (months)	Visual acuity at last exam	Visual retention index *	Classification of retinopathy at last exam	Degree of pituitary ablation
101.	R	29	F	W	9	26	20/25	$N_2F_2H_1$	3–65	1–67	22	20/30	15/15		Complete.
	L	--	--	--			HM	H_2				LP	0/15		
102.	R	40	F	W	3	38	20/400	$N_1F_1H_1$	4–65	12–66	20	LP	0/18		Partial.
	L	--	--	--			20/30	$N_2F_2H_1$				20/70	11/18		
103.	R	48	M	W	22	46	20/60	$N_1F_1H_0$	4–65	7–67	27	LP	13/18	$N_2F_2H_1$	Partial.
	L	--	--	--			20/40	$N_2F_2H_0$				LP	2/18	F_2H_2	
104.	R	29	M	W	7	29	20/20		4–65	12–66	20	20/50	12/20	$N_2F_2H_1$	None.
	L	--	--	--			20/200					20/400	20/20	$N_1F_2H_0$	
105.	R	30	M	W	12	29	20/20	$N_2F_1H_0$	4–65	7–66	15	20/20	15/15	$N_1F_1H_0$	Complete.
	L	--	--	--			NLP	$N_1F_2H_2$				Enuc			
106.	R	36	F	W	12	34	20/200	$N_1F_1H_0$	5–65	10–67	29	LP	0/12	H_2	Partial.
	L	--	--	--			LP	$N_1F_1H_0$				LP	0/12		
107.	R	41	M	W	12	38	20/100	$N_2F_2H_1$	5–65	6–68	37	20/60	37/37		Complete.
	L	--	--	--			20/200	$N_1F_2H_0$				20/60	37/37		
108.	R	37	M	W	15	34	20/20	$N_2F_1H_1$	5–65	1–68	32	20/30	21/21	$N_1F_1H_1$	Partial.
	L	--	--	--			NLP					NLP			
109.	R	28	F	W	14	27	20/20	$N_1F_0H_0$	5–65	1–68	32	20/25	23/23	$N_1F_1H_0$	Complete.
	L	--	--	--			20/25	$N_1F_0H_0$				20/40	23/23	$N_1F_1H_0$	
110.	R	28	M	W	15	26	20/30	$N_1F_2H_0$	5–65	10–67	29	20/200	5/13	H_0	None.
	L	--	--	--			CF	$N_2F_2H_1$				CF	13/13	H_1	
111.	R	29	F	W	9	22	HM		5–65	3–66	10	LP	0/10	$N_2F_2H_2$	N.A.
	L	--	--	--			LP					LP	0/10	$N_2F_2H_1$	
112.	R	23	F	W	7	21	LP	$N_2F_2H_1$	7–65		0				N.A.
	L	--	--	--			20/25	$N_2F_1H_0$							
113.	R	28	F	W	13	26	20/70	$N_2F_1H_0$	7–65	11–67	28	20/60	26/26	$N_2F_2H_0$	Partial.
	L	--	--	--			20/70	$N_2F_1H_0$				20/60	26/26	$N_2F_1H_1$	

114.	R L	52 --	M --	W --	25 ----	48 ----	20/60 NLP----	$N_2F_2H_1$ ----	7 65 ----	11–65 ----	4 ----	20/400---- NLP----	0/4 0/4	---- ----	Partial.
115.	R L	31 --	M --	W --	5 ----	29 ----	HM---- 20/25	---- ----	7–65 ----	---- ----	0 ----	---- ----	---- ----	---- ----	N.A.
116.	R L	41 --	M --	W --	29 ----	40 ----	20/50 20/400	$N_1F_1H_0$ $N_2F_1H_2$	7–65 ----	8–66 ----	13 ----	20/25---- HM----	11/11 0/11	$N_1F_1H_0$ H_2	Complete.
117.	R L	34 --	M --	W --	19 ----	29 ----	20/40 HM----	N_1F_2 F_2H_2	7–65 ----	10–66 ----	15 ----	20/40---- LP----	11/11 0/11	$N_1F_2H_1$ H_2	Complete.
118.	R L	48 --	M --	W --	20 ----	43 ----	20/30 20/200	$N_1F_2H_1$ $N_1F_2H_0$	7–65 ----	6–67 ----	23 ----	20/30---- 20/200----	16/16 16/16	H_1 H_0	Complete.
119.	R L	32 --	M --	W --	17 ----	31 ----	HM---- 20/70	N_1F_2 N_1F_2	8–65 ----	4–66 ----	8 ----	HM---- 20/40----	5/5 5/5	---- ----	Complete.
120.	R L	47 --	F --	W --	12 ----	46 ----	CF---- 20/25	H_2 $N_1F_1H_1$	8–65 ----	12–66 ----	16 ----	CF---- 20/40----	10/10 10/10	H_2 $N_1F_2H_1$	None.
121.	R L	56 --	F --	W --	35 ----	53 ----	20/400---- HM----	$N_2F_2H_0$ $N_2F_2H_1$	8–65 ----	3–68 ----	31 ----	15/200---- LP----	31/31 0/31	$N_1F_2H_1$ $N_2F_2H_0$	Partial.
122.	R L	46 --	M --	W --	35 ----	44 ----	HM---- 20/30----	---- $N_1F_1H_1$	9–65 ----	9–66 ----	12 ----	HM---- 20/70----	12/12 12/12	---- ----	None.
123.	R L	35 --	F ----	W ----	6 ----	31 ----	HM---- 20/200----	F_2 $N_2F_2H_1$	9–65 ----	4–67 ----	19 ----	HM---- 20/400----	19/19 19/19	---- $N_1F_2H_0$	Partial.
124.	R L	30 --	F ----	W ----	4 ----	29 ----	20/50---- HM----	---- ----	10–65 ----	6–66 ----	8 ----	---- ----	0/8 0/8	---- ----	Partial.
125.	R L	39 --	M ----	W ----	12 ----	32 ----	20/70---- 20/30----	$N_1F_1H_0$ $N_1F_1H_0$	10–65 ----	8–66 ----	10 ----	20/200---- 20/30----	5/10 10/10	$N_1F_1H_0$ $N_1F_1H_0$	Partial.
126.	R L	57 --	M ----	W ----	24 ----	50 ----	20/100---- 20/40----	N_1F_2 N_1F_1	10–65 ----	7–66 ----	9 ----	---- ----	---- ----	---- ----	Complete.
127.	R L	32 --	F ----	W ----	17 ----	31 ----	20/60---- CF----	---- ----	10–65 ----	1–66 ----	3 ----	15/200---- NLP----	0/3 0/3	$N_1F_1H_1$ ----	Partial.
128.	R L	45 --	F ----	W ----	13 ----	44 ----	20/20---- 20/25----	H_0 ----	10–65 ----	12–67 ----	26 ----	20/20---- HM----	12/12 7/12	$N_1F_1H_0$ H_0	Complete.
129.	R L	42 --	F --	W --	17 ----	41 ----	20/200---- 20/100----	$N_1F_2H_1$ $N_2F_2H_0$	10–65 ----	3–67 ----	17 ----	---- ----	---- ----	---- ----	N.A.

See footnote at end of table.

R. N. KJELLBERG, J. W. McMEEL, V. McMANUS, AND A. M. KOEHLER—Continued

Patient No.	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Date of last exam	Duration of followup (months)	Visual acuity at last exam	Visual retention index *	Classification of retinopathy at last exam	Degree of pituitary ablation
130.	R L	26 --	M --	W --	13	25	CF 20/30	$N_1F_2H_1$ $N_1F_1H_0$	12-65	12-66	12	20/400 20/80	12/12 11/12	H_1 $N_1F_1H_0$	Partial.
131.	R L	48 --	M --	W --	45	47	HM 20/50	F_2H_1 $N_1F_1H_1$	12-65	9-66	9				N.A.
132.	R L	47 --	M --	W --	15	46	20/20 20/20	$N_1F_0H_0$	12-65		0				N.A.
133.	R L	50 --	F --	W --	29	28	20/30 CF	$N_1F_1H_1$ H_1	2/66	12/66	10	Sustained do	3/3 3/3		Complete.
134.	R L	25 --	M --	W --	6	24	20/25 CF	$N_1F_1H_1$ N_1H_1	2/66	10/66	8	20/30 CF	8/8 8/8	$N_2F_2H_1$ $N_1F_2H_1$	None.
135.	R L	51 --	M --	W --	50	50	20/20 20/40	$N_1F_0H_0$ $N_2F_1H_0$	2/66	6/68	28	20/40 20/50	26/26 26/26	$N_1F_1H_1$ $N_1F_1H_0$	Complete.
136.	R L	30 --	M --	W --	13	27	20/50 20/50	$N_2F_2H_1$ $N_2F_2H_1$	2/66	7/66	5				N.A.
137.	R L	25 --	F --	W --	3	23	20/50 LP	$N_2F_2H_1$ H_2	2/66	12/66	10	LP LP	0/10 0/10		Partial.
138.	R L	47 --	M --	W --	31	45	HM 20/70	$N_1F_1H_0$ $N_1F_1H_0$	2/66	5/66	3				N.A.
139.	R L	51 --	M --	W --	7	48	20/30 HM	$N_1F_1H_0$ H_2	2/66	5/66	3				N.A.
140.	R L	50 --	F --	W --	10	49	20/200 20/40	$N_1F_1H_0$ $N_1F_1H_1$	2/66	9/66	7				None.
141.	R L	36 --	M --	W --	12	33	HM 20/25	F_2H_1 $N_1F_1H_0$	2/66	3/66	1	20/400 20/25	1/1 1/1	F_2H_0 $N_1F_1H_0$	N.A.
142.	R L	33 --	M --	W --	16	30	20/40 20/40	$N_2F_2H_1$ $N_1F_2H_1$	2/66	8/66	6	NLP NLP	0/6 4/6		Complete.

143.	R L	52 --	F --	W --	15 ----------	46 ----------	20/70 20/30	$N_2F_2H_1$ $N_2F_2H_1$	2/66 ----------	3/67 ----------	13 ----------	20/200 20/40	3/13 13/13	---------- ----------	Partial.
144.	R L	42 --	M --	W --	25 ----------	41 ----------	20/70 20/200	$N_2F_2H_1$ $N_1F_2H_1$	4–66 ----------	2–67 ----------	10 ----------	HM 20/60	0/10 10/10	$N_2F_2H_1$ $N_2F_2H_1$	Complete.
145.	R L	39 --	M --	W --	9 ----------	32 ----------	NLP 20/20	H_2 $N_2F_1H_1$	4–66 ----------	1–67 ----------	9 ----------	NLP 6/7	0/4 4/4	---------- $N_1F_1H_1$	None.
146.	R L	51 --	F --	W --	25 ----------	46 ----------	20/70 20/40	---------- ----------	4–66 ----------	11–67 ----------	19 ----------	20/40 20/200	19/19 9/19	$N_1F_1H_0$ $N_1F_2H_1$	Complete.
147.	R L	34 --	M --	W --	13 ----------	31 ----------	CF 20/70	H_1 $N_2F_2H_1$	5–66 ----------	9–66 ----------	4 ----------	HM HM	3/3 0/3	F_2H_1 $N_1F_2H_1$	N.A.
148.	R L	48 --	M --	W --	33 ----------	45 ----------	20/100 HM	$N_1F_1H_1$ $N_1F_2H_1$	5–66 ----------	7–66 ----------	2 ----------	---------- ----------	---------- ----------	---------- ----------	N.A.
149.	R L	49 --	M --	W --	28 ----------	48 ----------	20/70 20/25	$N_1F_1H_0$ $N_1F_1H_1$	5–66 ----------	11–66 ----------	6 ----------	---------- ----------	---------- ----------	---------- ----------	Partial.
150.	R L	48 --	M --	W --	45 ----------	46 ----------	20/50 20/30	$N_2F_1H_1$ $N_2F_1H_1$	5–66 ----------	9–66 ----------	4 ----------	20/70 20/30	1/1 1/1	$N_2F_1H_1$ $N_2F_1H_1$	N.A.
151.	R L	36 --	F --	W --	12 ----------	35 ----------	CF 20/30	H_2 $N_2F_2H_1$	5–66 ----------	1–67 ----------	8 ----------	LP HM	0/3 0/3	H_2 H_2	None.
152.	R L	48 --	F --	W --	12 ----------	45 ----------	20/25 20/50	---------- $N_1F_1H_0$	5–66 ----------	5–68 ----------	24 ----------	20/50 20/20	12/12 12/12	---------- ----------	Complete.
153.	R L	48 --	F --	W --	12 ----------	46 ----------	CF 20/40	H_2 H_1	6–66 ----------	12–66 ----------	6 ----------	---------- ----------	---------- ----------	---------- ----------	Complete.
154.	R L	58 --	F --	W --	41 ----------	57 ----------	20/40 HM	$N_2F_2H_0$ $N_2F_2H_1$	8–66 ----------	3–68 ----------	19 ----------	Sustained do	19/19 19/19	---------- ----------	N.A.
155.	R L	27 --	F --	W --	12 ----------	19 ----------	LP 20/400	$N_2F_2H_2$ $N_2F_2H_2$	8–66 ----------	9–66 ----------	1 ----------	---------- ----------	---------- ----------	---------- ----------	N.A.
156.	R L	45 --	M --	W --	22 ----------	42 ----------	20/70 20/50	$N_1F_2H_1$ F_2H_1	9–66 ----------	1–67 ----------	4 ----------	---------- ----------	---------- ----------	---------- ----------	Complete.
157.	R L	29 --	M --	W --	20 ----------	28 ----------	20/40 20/70	$N_2F_1H_0$ $N_2F_0H_0$	9–66 ----------	1–67 ----------	4 ----------	---------- ----------	---------- ----------	---------- ----------	N.A.

*Visual retention index = $\frac{\text{\# mos. vision sustained}}{\text{\# mos. patient followed}}$

Appendix F

O. H. PEARSON, C. I. THOMAS, ET AL.

(DATA FROM CHAPTER 28)

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy
1S. H.H.	R	58	M	W	38	56	20/600	$N_1F_2H_0$	2-28-61	Stalk section.
	L	--	--	--			LP	$N_1F_2H_0$		
2S. E. P.	R	31	F	W	13	31	LP	H_2	6-30-61	Stalk section.
	L	--	--	--			20/20	B		
3S. E. P.	R	41	M	W	12	36	LP	H_2	7-18-61	TF hypox.
	L	--	--	--			LP	Cataract		
4S. G. M.	R	20	F	W	4	19	15/30	$N_2F_0H_1$	11-10-61	TF hypox.
	L	--	--	--			LP	H_2		
5S. G. H.	R	34	F	W	10		CF	$N_1F_2H_0$	12- 5-61	TF hypox.
	L	--	--	--			20/30	$N_1F_0H_0$		
6S. G. F.	R	54	M	W	52	52	HM	$N_1F_2H_1$	4-24-62	TF hypox.
	L	--	--	--			HM	$N_1F_2H_1$		
7S. R. B.	R	25	M	W	4	23	20/25	$N_2F_0H_1$	11-19-64	TF hypox.
	L	--	--	--			NLP	H_2		
8S. A. D.	R	22	F	W	7	22	20/25	$N_2F_0H_0$	11-23-65	TF hypox.
	L	--	--	--			20/300	H_2		
9S. D. M.	R	26	M	W	12	22	2/400	H_2	12-31-65	TF hypox.
	L	--	--	--			5/400	H_2		
10Y. R. R.	R	22	M	W	7	21	20/20	$N_2F_1H_1$	1-30-63	Y90 hypox.
	L	--	--	--			LP	H_2		
11Y. W. M.	R	61	F	W	36	57	LP	$N_1F_2H_0$	2- 5-63	Y90 hypox.
	L	--	--	--			20/200	$N_1F_2H_0$		
12Y. H. S.	R	46	M	N	30	42	20/40	$N_1F_0H_0$	2- 5-63	Y90 hypox.
	L	--	--	--			20/30	B		
13.Y W. K.	R	42	M	W	15	38	20/200	$N_2F_2H_1$	3-19-63	Y90 hypox.
	L	--	--	--			NLP	Cataract		
14Y. R. S.	R	39	M	W	15	36	20/40	$N_1F_2H_1$	3-19-63	Y90 hypox.
	L	--	--	--			LP	H_2		
15Y. E. M.	R	56	F	W	23	52	20/400	$N_1F_2H_1$	6- 7-63	Y90 hypox
	L	--	--	--			LP	H_2		
16Y. P.	R	47	M	W	36	47	20/25	B	6-28-63	Y90 hypox.
	L	--	--	--			20/40	B		
17Y. J. H.	R	36	M	W	14	31	20/200	$N_1F_2H_1$	7-11-63	Y90 hypox.
	L	--	--	--			Enucleated			
18Y. E. S.	R	61	F	W	36	60	20/40	$N_1F_0H_1$	7-12-63	Y90 hypox.
	L	--	--	--			20/40	$N_1F_0H_1$		
19Y. V. S.	R	58	F	W	57	57	20/400	$N_2F_0H_1$	8-29-63	Y90 hypox.
	L	--	--	--			20/60	$N_2F_0H_1$		

Date of last exam	Duration of follow-up (months)	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Degree of pituitary ablation	Complications	Remarks
5-68	87	20/100	1.0	$N_0F_2H_0$	Complete	None	Died 6-68, coronary.
		LP	1.0	$N_0F_2H_0$			
3-62	8	20/40	1.0	B	?	None	Died 3-62, coronary.
		20/15	1.0	B			
7-66	60+	LP	0	Cataract	Complete	None	Living 5 plus years.
		NLP	0	Enucleated			
11-63	24	20/30	1.0	B	Complete	None	Died 11-63 suicide.
		LP	1.0	H_2			
4-63	27	LP	0	$N_1F_2H_1$	Complete	None	Died 2-64, heart failure.
		20/40	1.0	$N_1F_0H_0$			
6-68	74	20/200	1.0	$N_0F_2H_0$	Complete	None	Living.
		20/200	1.0	$N_0F_2H_0$			
7-68	44	LP	0.6	$N_2F_2H_2$	Incomplete +.	None	7-7-66, reoperation. Blind since 3-6-67.
		NLP		H_2			
12-65	9	20/25	1.0	$N_1F_2H_0$	Complete	None	Died 8-66, hypoglycemia.
		20/70	1.0	$N_1F_2H_1$			
6-13-66	18	HM	1.0	H_2	Complete	None	Died 6-5-67.
		20/200+	1.0	$N_2F_0H_1$			
1-64	12	LP	0.5	H_2	Incomplete +.	None	Reoperation, 1-30-64.
		LP	0	H_2	10 percent residual.		Post op death, 2-7-64.
2-66	46	LP	0	$N_1F_2H_0$	Complete	None	Died, heart failure.
		20/70	1.0	$N_0F_2H_0$			
7-9-64	21	20/50	0.9	B	Complete	Transient rhinorrhea.	Died 11-64, cerebral thrombosis.
		20/40	1.0	B			
2-24-65	36	20/60	1.0	$N_0F_2H_0$	Complete	None	Died 4-5-66, coronary.
		NLP		Cataract			
1-22-64	15	20/30	1.0	$N_0F_2H_0$	Complete	None	Died 6-19-64, coronary.
		CF	0	H_2			
3-1-64	45	20/200	0.5	$N_1F_2H_1$	Complete	Diabetes insipidus.	Died 3-4-67, pulmonary embolus.
		LP	0	H_2			
5-19-65	30	20/25	1.0	B	Complete	Meningitis	Died 1-25-66, cardiac arrest.
		20/15	1.0	B			
6-21-65	60+	LP	0	H_2	Incomplete ++.	None	Living.
		Enucleated					
7-8-67	50	20/50	1.0	$N_1F_0H_0$	? Complete	Transient 3d nerve palsy.	Died 8-17-67, coronary.
		20/50	1.0	$N_1F_0H_0$			
12-21-66	42	20/100	1.0	$N_0F_0H_0$	Complete	None	Died 2-10-67, coronary.
		20/40	1.0	$N_0F_0H_0$			

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy
20Y. P. P.	R	35	M	W	11	32	LP	H_2	12-12-63	Y90 hypox.
	L	--	--	--			20/300	$N_1F_1H_1$		
21Y. F. C.	R	30	M	W	14	29	Enucleated.		12-12-63	Y90 hypox.
	L	--	--	--			CF	$N_2F_1H_1$		
22Y. E. H.	R	66	F	W	51	63	LP	$N_2F_2H_1$	1- 9-64	Y90 hypox.
	L	--	--	--			CF	$N_2F_2H_1$		
23Y. E. W.	R	40	F	N	38	39	10/400	$N_2F_1H_1$	1-30-64	Y90 hypox.
	L	--	--	--			25/400	$N_2F_1H_1$		
24Y. A. M.	R	64	F	W	49	63	20/70	$N_1F_0H_0$	3-19-64	Y90 hypox.
	L	--	--	--			20/50	$N_1F_0H_0$		
25Y. C. G.	R	27	M	W	4	27	20/40	$N_1F_0H_0$	3-26-64	Y90 hypox.
	L	--	--	--			20/40	$N_1F_0H_0$		
26Y. T. B.	R	57	M	N	38	55	5/400	$N_1F_2H_0$	6-11-64	Y90 hypox.
	L	--	--	--			20/90	$N_1F_2H_0$		
27Y. M. B.	R	24	F	W	12	23	20/50	$N_2F_1H_1$	6-25-64	Y90 hypox.
	L	--	--	--			CF	$N_2F_2H_1$		
28Y. A. D.	R	48	M	W	46	46	20/200	$N_2F_0H_1$	7-23-64	Y90 hypox.
	L	--	--	--			20/30	$N_2F_1H_1$		
29Y. V. T.	R	32	M	W	13	30	CF	$N_1F_2H_0$	9-17-64	Y90 hypox.
	L	--	--	--			20/25	$N_1F_2H_1$		
30Y. C. I.	R	31	M	W	13	28	CF	$N_1F_2H_1$	10-28-64	Y90 hypox.
	L	--	--	--			20/300	$N_1F_2H_1$		
31Y. R. S.	R	35	M	W	13	31	20/70	$N_1F_1H_1$	10-29-64	Y90 hypox.
	L	--	--	--			CF	$N_1F_2H_1$		
32Y. A. B.	R	62	F	W	32	59	20/60	$N_1F_1H_1$	12 -3-64	Y90 hypox.
	L	--	--	--			LP	$N_1F_2H_1$		
33Y. N. W.	R	52	F	W	35	49	CF	$N_1F_2H_1$	12-10-64	Y90 hypox.
	L	--	--	--			LP	H_2		
34Y. B. C.	R	56	M	W	39	51	LP	$N_1F_2H_1$	1-14-65	Y90 hypox
	L	--	--	--			20/300	$N_1F_0H_1$		
35Y. R. W.	R	36	M	W	11	34	LP	$N_1F_2H_1$	4-17-65	Y90 hypox
	L	--	--	--			20/20	$N_1F_1H_1$		
36Y. A. G.	R	60	F	W	52	56	LP	$N_1F_2H_1$	4- 1-65	Y90 hypox
	L	--	--	--			10/200	H_2		
37Y. A. F.	R	51	F	W	46	51	20/20	$N_1F_0H_1$	4-29-65	Y90 hypox
	L	--	--	--			20/200	$N_1F_0H_1$		
38Y. J. C.	R	34	M	W	13	30	LP	$N_2F_2H_1$	7- 8-65	Y90 hypox
	L	--	--	--			LP	$N_2F_2H_1$		
39Y. I. B.	R	41	F	W	21	40	20/60	$N_1F_1H_1$	9-16-65	Y90 hypox
	L	--	--	--			LP	$N_1F_2H_1$		

THOMAS, ET AL—Continued

Date of last exam	Duration of follow-up (months)	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Degree of pituitary ablation	Complications	Remarks
11–13–67	57	NLP 20/300	0 1.0	$N_0F_2H_0$ $N_0F_1H_0$	Complete	None	Living.
12–14–65	14	Enucleated CF	 0	 $N_1F_2H_1$	Complete	None	Died 2–14–65, uremia.
6–19–67	54	LP HM	0 0	$N_2F_2H_0$ $N_2F_2H_0$	Complete	None	Living.
5–68	54	20/50 20/300	1.0 1.0	$N_0F_2H_0$ $N_0F_2H_0$	Complete	None	Living.
7–68	51	LP 20/50	0.5 1.0	Cataract $N_0F_0H_0$	? Complete	None	Living.
7–68	51	20/25 20/15	1.0 1.0	$N_0F_0H_0$ $N_0F_0H_0$	Complete	None	Living.
7–68	48	LP 20/70	0 1.0	$N_1F_2H_0$ $N_1F_2H_0$	Complete	None	Living, cataracts removed o.u.
7–68	48	20/15 20/70	1.0 1.0	$N_0F_1H_0$ $N_0F_2H_0$	Complete	Transient rhinorrhea.	Living.
7–68	48	LP 20/25	0 1.0	Cataract $N_0F_1H_0$	Complete	None	Living.
6–68	45	CF 20/400	0 0.27	$N_0F_2H_0$ $N_0F_2H_0$	Complete	None	Living.
5–68	43	LP 20/200	0 1.0	$N_0F_2H_1$ $N_0F_2H_0$	Complete	None	Died 5–68.
1–67	26	20/20 LP	1.0 0	$N_0F_1H_0$ $N_0F_2H_0$	Complete	Rhinorrhea	Died 1–3–67 berry aneurysm.
2–67	30	LP LP	0.5 0.5	Cataract do	Complete	Transient rhinorrhea.	Died 5–67, coronary.
8–67	32	CF LP	0 0	$N_1F_2H_0$ H_2	Complete	None	Died 8–7–67, coronary.
2–65	1	CF 20/200	 	$N_1F_2H_1$ $N_1F_0H_1$	Complete	None	Died 2–14–65, cerebral edema.
11–67	41	LP 20/200	0 0.2	$N_0F_2H_0$ $N_0F_2H_0$	Complete	None	Living.
9–8–65	36	10/400 10/400	0 0	$N_1F_2H_1$ H_2	Complete	None	Living.
6–68	38	NLP 20/70	0.63 1.0	Cataract $N_1F_0H_1$	Complete	Rhinorrhea, intrasellar hemorrhage.	Living.
9–20–67	36	20/50–1 LP	1.0 1.0	$N_0F_2H_0$ H_2	Complete	None	Living.
11–29–66	36	20/30 20/70	1.0 1.0	$N_0F_1H_0$ $N_0F_2H_0$	? Complete	None	Living.

O. H. PEARSON, C. I.

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy
40Y. H. F.	R	67	M	W	67	67	20/60	B	9–23–65	Y90 hypox
	L	--	--	--			CF	H_2		
41Y. R. A.	R	62	F	W	57	62	20/40	$N_1F_0H_1$	9–23–65	Y90 hypox
	L	--	--	--			LP	$N_1F_2H_1$		
42S. R. T.	R	39	F	W	22	39	20/30	$N_1F_1H_1$	1– 6–66	TS hypox
	L	--	--	--			20/70	$N_2F_2H_1$		
42S. R. T.	R	39	F	W	22	39	20/40	$N_1F_2H_1$	7–22–66	TS hypox
	L	--	--	--			20/40	$N_1F_2H_1$		
43S. E. H.	R	63	F	N	46	60	20/50	$N_1F_0H_0$	1–28–66	TS hypox
	L	--	--	--			20/50	$N_1F_0H_0$		
44S. L. B.	R	33	F	W	11	32	LP	$N_2F_1H_1$	2– 6–66	TS hypox.
	L	--	--	--			LP	$N_2F_1H_1$		
45S. F. S.	R	28	M	W	31	36	LP	H_2	3–4–66	TS hypox.
	L	--	--	--			20/40	$N_2F_0H_1$		
46S. E. N.	R	37	M	W	15	32	LP	$N_1F_2H_1$	4– 8–66	TS hypox.
	L	--	--	--			20/25	$N_1F_0H_1$		
47S. P. G.	R	36	F	W	17	33	20/20	$N_1F_0H_0$	7–22–66	TS hypox.
	L	--	--	--			20/20	$N_1F_0H_0$		
48S. B.	R	47	F	W	27	39	20/200	$N_2F_1H_2$	11–26–66	TS hypox.
	L	--	--	--			20/200	F_2H_2		
49S. A. C.	R	59	F	W	40	57	20/200	$N_1F_0H_0$	8– 4–67	TS hypox.
	L	--	--	--			20/200	$N_1F_0H_0$		
50S. W.	R	43	M	W	25	12	20/300	$N_1F_2H_1$	8–10–67	TS hyopx.
	L	--	--	--			LP	$N_1F_0H_1$		
51S. R. V.	R	24	M	W	10	22	20/60	$N_2F_1H_1$	10–20–67	TS hypox.
	L	--	--	--			20/25+	$N_2F_0H_1$		
52S. R. S.	R	21	M	W	9	21	20/40–1	$N_2F_0H_1$	4– 2–68	TS hypox.
	L	--	--	--			LP	H_2		

NOTE.—Patients 1–9 had transfrontal craniotomy.
Patients 10–41 had transnasal transsphenoidal yttrium 90 implants.
Patients 42–52 had sublabial transnasal transsphenoidal hypophysectomy.

THOMAS, ET AL—Continued

Date of last exam	Duration of follow-up (months)	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Degree of pituitary ablation	Complications	Remarks
	9				? Complete	Meningitis	Died.
7-68	34	20/50	1.0	$N_1F_2H_1$	Complete	Transient rhinorrhea.	Living.
		LP	0	$N_1F_2H_0$			
7-21-66	6	20/40	1.0	$N_1F_2H_1$	Incomplete ++++.	None	Living.
		20/40	1.0	$N_1F_2H_1$			
5-27-68	24	10/200	0.8	$N_0F_2H_0$	Incomplete +.	None	Living.
		LP	0.5	$N_0F_2H_0$			
7- 8-68	30	20/200		$N_0F_2H_0$	Incomplete +++.	None	Living, photocoagulation.
		20/50	1.0	$N_0F_2H_0$			
6-17-68	30	20/70+1	1.0	$N_1F_2H_0$	Complete	None	Living.
		20/100	1.0	$N_1F_2H_0$			
7-68	28	NLP	0	H_2	Incomplete +.	Rhinorrhea reoperation.	Living.
		20/30	1.0	$N_0F_1H_0$			
3-24-67	11	NLP	0	$N_1F_2H_0$	? Complete	None	Living.
		20/30	1.0	$N_1F_0H_1$			
7-68	24	20/20	1.0	$N_0F_0H_0$	Complete	None	Living.
		20/20	1.0	$N_0F_0H_0$			
1-67	2				Complete	Rhinorrhea	Died 1-67, pneumonia.
6-68	10	20/100+1	1.0	$N_0F_0H_0$	Complete	None	Living.
		20/100+1	1.0	$N_0F_0H_0$			
3-68	7	20/70	1.0	$N_0F_2H_0$	Complete	None	Living.
		HM	1.0	$N_0F_0H_0$			
5-68	7	20/200		$N_1F_2H_0$	Complete	None	Living.
		20/15	1.0	$N_1F_1H_0$			
7-68	3	20/30-2	1.0	$N_1F_0H_1$	? Complete	None	Living.
		HM	1.0	H_2			

Appendix G–1

N. ROTH AND R. W. RAND

(DATA FROM CHAPTER 29)

[Mode of therapy—CRYOHYPOPHYSECTOMY]

Patient number	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Date of last exam	Duration of followup (months)	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Degree of pituitary ablation	Complications	Results[1]
1.	R	31	M	C			HM		8- 5-63	7-65	24	6/200	24/24		C	Death at 25 months, renal failure.	I
	L	--	--	--			20/40					20/100	24/24				
2.	R	40	M	C	20	34	20/60–2	$N_2F_2H_1$	1-20-64	2-26-68	49	20/40	49/49	$N_1F_2H_0$	C	None	I
	L	--	--	--			20/20	$N_1F_0H_0$				20/20	49/49				
3.	R	27	M	C			20/30		2- 3-64	12-66	34	20/20	34/34		Borderline		I
	L	--	--	--			5/200					20/100	34/24				
4.	R	47	M	C			20/50		4-30-64	5-67	37	HM	4/52		C		P
	L	--	--	--			HM					NLP	4/52				
5.	R	47	M	C	28	42	20/40–1	$N_1F_1H_1$	9-17-64	5-31-67	32	20/30	32/32	$N_1F_1H_0$	C	Died 11-14-67, cause unknown.	I
	L	--	--	--			20/100	$N_1F_1H_1$				20/40–2	32/32	$N_1F_1H_0$			
6.	R	52	F	C	22	44	LP	$N_2F_2H_1$	11- 2-64	8-10-68	45	20/100	45/45	$N_1F_2H_0$	C	None	I
	L	--	--	--			20/50	$N_2F_2H_1$				20/40	45/45	$N_1F_2H_0$			
7.	R	47	F	C	12	39	20/30	$N_1F_0H_1$	3-22-65	3-68	36	20/30	33/33	$N_1F_0H_0$	C	None	I
	L	--	--	--			HM–2′	$N_1F_1H_1$				HM–2′	33/33	$N_1F_1H_0$			
8.	R	58	M	C	38	56½	Nil		4- 5-65	7-65	4½	Nil	3/3		C	Expired 4½ months post-operative.	I
	L	--	--	--			20/100–1					20/40	3/3				

9.	R L	-- --	M --	C --	9 ---	30 ---	20/25 20/25	$N_2F_1H_0$ $N_2F_1H_0$	7–19–65 ---	6–67 ---	23 ---	20/20 20/20	23/23 23/23	$N_1F_1H_0$ $N_1F_1H_0$	C ---	None ---	I
10.	R L	55 --	M --	C --	52 ---	52 ---	20/200 20/400	$N_1F_0H_0$ $N_1F_0H_0$	11– 5–65 ---	7–11–67 ---	20 ---	20/25–2 20/400	20/20 20/20	$N_1F_0H_0$ $N_1F_0H_0$	C ---	None ---	I
11.	R L	34 --	F --	C --	13 ---	31 ---	20/80 20/70	$N_2F_2H_1$ $N_2F_2H_2$	7–26–65 ---	--- ---	30 ---	20/50, 20/200. CF	8/30 12/30	$N_2F_2H_0$ $N_2F_2H_0$	C ---	Died, coronary artery disease.	P
12.	R L	28 --	M --	C --	7 ---	23½ ---	20/60 20/200	$N_1F_1H_1$ $N_1F_2H_1$	11– 5–66 ---	4– 5–66 ---	16 ---	HM—3′ 20/200	5/16 5/16	F_2H_2 F_2H_2	C ---	Recurrent vitreous hemorrhages.	P
13.	R L	42 --	F --	C --	24 ---	39 ---	20/100 20/20	--- ---	3–11–66 ---	11–67 ---	19 ---	20/40, 20/200. 20/70, 20/200.	3/19 3/19	--- ---	C --- C ---	--- ---	
14.	R L	29 --	F --	(2) --	9 ---	26 ---	20/400 20/200	H_2 H_2	5– 6–66 ---	5–68 ---	24 ---	20/40 20/40	24/24 24/24	BH_0 BH_0	C ---	None ---	I
15.	R L	34 --	M --	C --	14 ---	32 ---	20/100 20/50+4	$N_1F_2H_1$ $N_1F_2H_1$	8– 8–66 ---	8–19–68 ---	24 ---	20/80+1 20/50+1	24/24 24/24	$N_1F_1H_0$ $N_1F_1H_0$	C ---	None ---	I
16.	R L	52 --	M --	C --	--- ---	--- ---	20/200 LP	$N_2F_1H_1$ $N_2F_1H_1$	2– 5–67 ---	2–28–67 ---	10 ---	20/100 20/100	10/10 10/10	$N_2F_1H_1$ $N_2F_1H_1$	C ---	None ---	S
17.	R L	35 --	M --	C --	10 ---	31 ---	LP 20/30	$N_2F_2H_1$ $N_2F_1H_1$	6–28–67 ---	4– 4–68 ---	14 ---	LP CF–2′	3/14 3/14	$N_2F_2H_1$ $N_2F_2H_1$	I ---	Inappropriate antidiuretic hormone. syndrome.	P
18.	R L	40 --	F --	C --	24 ---	39 ---	20/50 LP	--- ---	7–11–67 ---	8–8–67 ---	12 ---	20/40 LP	8/8 8/8	--- ---	C ---	Drill broke	I
19.	R L	47 --	F --	C --	19 ---	37 ---	20/400 20/50–2	$N_1F_2H_1$ $N_1F_2H_1$	9–12–67 ---	7–67 ---	10 ---	20/60+2 20/50	10/10 10/10	$N_1F_2H_0$ $N_1F_2H_0$	C ---	Hypoglycemia from DBI.	I
20.	R L	43 --	M --	C --	28 ---	42 ---	20/30 20/60–1	$N_2F_0H_1$ $N_2F_0H_1$	2–13–68 ---	8–68 ---	6 ---	20/25–2 20/200	6/6 1/6	$N_2F_0H_0$ $N_2F_0H_2$	C ---	DI	S
21.	R L	28 --	F --	C --	7 ---	27 ---	CF 20/20	$N_2F_2H_1$ $N_2F_2H_1$	2–19–68 ---	7–68 ---	5 ---	20/200 20/20	5/5 5/5	$N_2F_1H_0$ $N_2F_1H_0$	Delayed 3 months C. ---	--- ---	I
22.	R L	48 --	F --	C --	30 ---	47 ---	20/60 20/100	$N_2F_1H_1$ $N_2F_1H_1$	3–11–68 ---	8–12–68 ---	5 ---	CF—3′ 20/40–1	2/5 5/5	$N_1F_1H_0$ $N_1F_1H_1$	C ---	None ---	I

See footnotes at end of table.

N. ROTH AND R. W. RAND—Continued

Patient number	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Date of last exam	Duration of followup (months)	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Degree of pituitary ablation	Complications	Results [1]
23.	R	46	M	C	26	45	20/100	$N_2F_2H_1$	5-6-68								
	L	--	--	--			HM	$N_2F_2H_1$									
24.	R	39	M	C	12	34	CF—4′	H_2	5-13-68	7-23-68	3	HM—2′	3/3	F_2H_2	C	None	S
	L	--	--	--			HM—½′	F_2H_2				HM—6″	3/3	F_2H_2			
25.	R	27	F	C	13	26	20/50	$N_1F_1H_1$	6- 4-68	7-29-68	2	20/40—1	2/2	$N_1F_1H_0$	C	Perforated turbinate, severe epistaxis & rhinorrhea.	I
	L	--	--	--			HM—2′	$N_1F_2H_1$				HM—3′	2/2	$N_1F_1H_0$			
26.	R	32	M	C	10	32	20/40—1	$N_2F_2H_1$	6-11-68	8-68	2	20/40—1	2/2	$N_2F_2H_1$	C		S
	L	--	--	--			CF	$N_2F_2H_1$				FC	2/2	$N_2F_2H_1$			
27.	R	38	M	C	17	34	20/100—1		8- 1-68						C	None	
	L	--	--	--			20/25—2										
28.	R	32	F	C	9	30½	20/40—2	$N_2F_2H_1$	8-14-68						C		
	L	--	--	--			20/400	H_2									
29.	R	44	F	N	18	42	20/30—1	$N_2F_0H_0$	8- 4-68		1				C	None	
	L	--	--	--			HM—6′	$N_2F_0H_0$									
30.	R	--	M	C			20/200		6-10-65	9-15-66	3	20/70	3/3		C	None	I
	L	--	--	--			20/100					20/30	3/3				

[1] I=improved; S=stable; P=progressed.
[2] American Indian.

Appendix G–2

N. ROTH AND R. W. RAND

Patient No.	Insulin [1] (units)		PBI (ugm/100ml)		Percent radioactive iodine uptake (6/24 hour)		T3 (percent)		FSH (mu)		PAP smear estrogen		Growth [2] hormone (ugm/100ml)		Post-op meds [3]
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
1	L44; SL12	L28; SL10	3.9	4.2	/19.7	/4.8			Under 7.2	Under 8.8					A; T.
2	L32; R8	L12; UL12; R4	4.2	3.7	/13.1	/6.2			7.6	Under 6					A; T.
3	N25; R15	N20 (a.m.); N10 (p.m.)	5.9	3.9	/20.3	/11.1			Under 6	Under 6					A.
4	N60	L35	5.5	3.2	/28.2	/9.0			6.6	Under 6.6					A; Test.
5	N15; R10	N12	4.3	3.0	/13.6	/10.1			Under 6	Under 6					A; Test.
6	N40	N15	4.7	2.8	4/	0/			13	50					A; Est.
7	L12; UL4; R16	L16; UL6	4.8	2.9	/14.9	/4.8			Under 14	8					A; T; ADH.
8	N40	N22	5.7	2.8	/20.2	/5.1			5.7	17					A.
9	L34	L32.0	5.5	4.9	/19.1	/3.1			66	23					A.
10	O R 3 gm	DIAB 250 mg	5.8	2.0	/18	/1			6–50	Under 16					A; T; Test.
11	L20	L12	5.5	4.6	/23.6	?				6–50					A; T; Est.
12	L25	L25	3.8	3.4	/15	/4			15	4					A; T.
13	L55	L15	6.7	3.8	/18	/5			Under 6	Under 8				(I); under 2.	A; T; Est.
14	N30	N16	5.2	3.6	/18	/8			16	39					A; T; Est.

See footnotes at end of table.

N. ROTH AND R. W. RAND—Continued

Patient No.	Insulin [1] (units)		PBI (ugm/100ml)		Percent radioactive iodine uptake (6/24 hour)		T3 (percent)		FSH (mu)		PAP smear estrogen		Growth [2] hormone (ugm/100ml)		Post-op meds [3]
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
15	N44	N13	3.8	.....	/19	/1.9	.....	.....	.....	Under 6	.....	.....	.....	.....	A; T; Test.
16	DIAB 500	DIAB 125	5.3	5.3	/14	/4.1	.....	.....	6–50	Under 5	.....	.....	.....	.....	A; T; Test.
17	L45; R5	L35	6.0	5.0	8.7/17.7	7.5/11.2	31	.....	.....	.....	.....	.....	.....	IN: (blunted).	A.
18 (1st hospital)	N40	N30	4.4	3.3	7/16	.....	.....	.....	Under 16	.....	Good	.....	.....	.....	A.
18 (2d hospital)	N30	N20	4.5	.....	.....	4.0/6.4	.....	.....	.....	.....	.....	.....	.....	.....	A.
19	N10	N8	5.6	3.0	19/45	2/5	.....	.....	.....	16–50	Fair	None	.....	.....	A; T.
20	N70	N35	4.4	3.1	7/14	1/4	32	.....	16–50	Under 6	.....	.....	.....	.....	A; T.
21	N30	N18	4.2	2.0	4/8;/14	5/12	27	.....	Under 6	Under 6	Good	.....	.....	.....	A; T.
22	N40	N20	5.4	2.2	11/21	1/1	.....	.....	Under 100	16–50	.....	.....	.....	.....	A; T.
23	N20; R15(A); N15(P).	N20	13	.....	5.2/4.9	.....	28	.....	.....	.....	.....	.....	.....	.....	A.
24	N40	N25	(4)	(4)	7/8	/1	.....	18	16–50	Under 16	.....	.....	IN: 2 to 5	.....	A; T; Test.
25	N16(a.m.) R8; N5(p.m.); R5.	N14; R6	7.2	3.8	9/24	2/2.1	26	.....	Under 50	.....	Good	.....	IN: 5 to 18.	.....	A; T; Test.
26	N70	N30	3.4	3.0	8/13	5/1	31	.....	6–16	Under 6	.....	.....	IN: 2 to 14 AR: 2 to 45.	.....	A; T; Test.
27	N40(A); N20(P).	N45	6.8	.....	4/7	.....	35	.....	.....	.....	.....	.....	AR: 12 to 23.		

[1] L=Lente; SL=Semilente; UL=Ultralente; N=NPH; R=Regular; OR=Orinase; DIAB=Diabinese.
[2] IN=IV insulin test; AR=Arginine infusion.
[3] A=Adrenal steroids; T=Thyroid; Test=Testosterone; Est.=Estrogen; ADH=Antidiuretic hormone.
[4] Too high to read.

Appendix H

J. H. DOBREE

(DATA FROM CHAPTER 37)

[Mode of therapy—LIGHT COAGULATIONS]

Number and patient	Eye	Age	Sex	Race	Age at onset	Age at 1st ocular symptom	Visual acuity, pretreatment	Classification of retinopathy pretreatment	Date of therapy	Date of last exam	Duration of followup (months)	Visual acuity at last exam	Visual acuity retention	Classification of retinopathy at last exam	Complications and notes
1. G. B.	L	61	F	C	42	56	2/60	$N_2F_2H_1$	10–66	5–68	19	LP	13/19	H_2	Rubeosis.
2. M. B.	L	55	F	C	45	46	6/24	$N_2F_1H_0$	10–64	3–68	49	HM	17/49	H_2	
3. H. B.	L	38	M	C	25	37	6/5	$N_1F_1H_0$	----------	7–68	----------	3/60	----------	$N_0F_2H_0$	
4. V. B.[1]	R	41	F	C	12	40	6/12	$N_1F_0H_1$	2–67 (2)	8–68	18	3/60	10/18	$N_0F_2H_1$	
5. J. C.	R	46	M	C	15	42	6/6	$N_1F_2H_0$	11–64	7–68	47	6/6	47/47	$N_2F_2H_0$	
6. C.	R	43	M	C	8	33	6/9	$N_2F_1H_0$	5–67	7–68	15	6/9	15/15	$N_0F_2H_0$	
7. J. C.	L	28	F	C	11	21	6/9	$N_2F_0H_0$	2–68	7–68	6	6/9	6/6	$N_0F_0H_0$	
8. J. C.	R	24	F	C	3	24	6/6	$N_2F_0H_0$	6–66 (3)	6–68	24	6/6	24/24	$N_0F_0H_0$	
9. F.	R	47	M	C	35	41	6/9	$N_1F_2H_1$	5–63	9–63	6	HM	6/63	H_2	Inadequate treatment.
10. G.[2]	L	66	F	C	59	59	6/24	$N_2F_0H_1$	6–67	8–68	14	6/60	6/14	$N_0F_0H_1$	
11. H.	R	56	M	C	35	53	6/12	$N_2F_2H_1$	10–67	7–68	20	1/60	2/9	H_2	
12. J. J.	L	58	M	C	48	50	6/6	$N_2F_0H_0$	6–67	7–68	14	1/60	6/12	H_2	May clear.
13. Ja.	L	63	F	C	38	61	HM	$N_2F_1H_1$	5–67	5–68	12	6/6	12/12	$N_1F_2H_0$	
14. Jo.	R	32	F	C	17	31	6/6	$N_2F_0H_0$	11–67	8–68	9	6/6	9/9	$N_0F_0H_0$	
	L	--	--	--	----------	----------	6/36	$N_2F_0H_0$	11–67	8–68	9	6/36	9/9	$N_0F_0H_0$	

See footnotes at end of table.

J. H. DOBREE—Continued

Number and patient	Eye	Age	Sex	Race	Age at onset	Age at 1st ocular symptom	Visual acuity, pretreatment	Classification of retinopathy pretreatment	Date of therapy	Date of last exam	Duration of followup (months)	Visual acuity at last exam	Visual acuity retention	Classification of retinopathy at last exam	Complications and notes
15. B. J.	L	34	M	C	2	32	6/36	$N_1F_2H_0$	10–63	3–65	15	1/60	6/15	----------	Died.
16. Ke.	R	46	M	C	22	42	6/24	$N_1F_2H_1$	6–64	6–68	51	LP	1/51	H_2	Retinal detachment.
17. Ki.	R	54	F	C	47	50	6/6	$N_2F_1H_1$	12–67	8–68	8	6/6	8/8	$N_1F_1H_0$	
18. R. L.	R	54	F	C	27	45	6/12	$N_2F_2H_1$	6–63	7–68	66	HM	11/61	H_2	
	L	—	—	—	----------	----------	6/12	$N_2F_2H_0$	6–63	7–68	66	2/60	11/61	$N_1F_2H_1$	
19. M.	R	51	M	C	24	52	6/6	$N_1F_0H_0$	3–67 (2)	7–68	16	6/6	16/16	$N_0F_1H_0$	Macula burn.
	L	--	--	--	----------	----------	6/6	$N_1F_0H_0$	10–67 (2)	----------	9	6/18	0/9	$N_0F_1H_0$	
20. P. M.	R	51	F	C	38	48	6/6	$N_1F_2H_0$	3/66	6–68	27	6/9	27/27	$N_0F_2H_0$	
21. A. M.	L	63	M	C	56	61	6/9	$N_2F_0H_0$	1–67	6–68	18	6/12	12/18	$N_0F_1H_1$	
22. S. M.	L	48	M	C	16	48	6/9	$N_1F_0H_0$	7–63	8–68	66	HM	14/61	$N_0F_2H_1$	
23. D. P.	L	61	F	C	53	58	6/12	$N_2F_1H_0$	10–66	7–68	9	HM	2/9	----------	Arterial occlusion; rubeosis.
24. B. P.	L	48	M	C	19	45	6/9	$N_1F_1H_0$	1–67	7–68	20	6/12	18/20	$N_1F_1H_1$	
25. B. R.	L	45	F	C	35	39	6/6	$N_1F_0H_0$	10–67	8–68	72	6/6	10/10	$N_1F_1H_0$	
26. J. R.	L	53	M	C	45	50	6/9	$N_1F_1H_0$	9–66	6–68	22	6/9	22/22	$N_1F_1H_0$	
27. C. R.	R	20	M	C	4	15	6/9	$N_2F_0H_0$	4–65	4–68	36	HM	2/36	H_2	
28. S. S.	R	52	M	C	35	31	6/6	$N_1F_0H_0$	2–68	7–68	6	6/6	6/6	$N_0F_0H_0$	
	L	--	--	--	----------	----------	6/6	$N_1F_0H_0$	5–66	----------	27	6/6	27/27	$N_1F_0H_0$	
29. T. S.	R	54	M	C	45	53	6/6	$N_1F_1H_0$	10–66	9–67	12	6/6	11/11	$N_0F_1H_0$	
30. H. W.	L	68	M	C	58	54	6/18	$N_1F_0H_0$	2–67	6–68	16	6/24	8/16	$N_1F_2H_1$	
31. Mc.	R	46	M	C	23	45	6/6	$N_1F_1H_0$	9–67	8–68	11	6/24	4/11	$N_1F_1H_1$	

32. H	R	42	M	C	39	40	6/6	$N_2F_0H_0$	1–68	7–68	6	6/6	6/6	$N_0F_0H_0$	Macular burn.
	L	--	--	--			6/12	$N_2F_0H_0$	1–68	7–68	6	6/18	0/6	$N_0F_0H_0$	
33. S	R	63	M	C	48	62	6/18	$N_2F_0H_0$	12–67	7–68	7	6/18	7/7	$N_0F_0H_0$	
	L	--	--	--			6/18	$N_2F_0H_0$	1–68	7–68	6	6/18	6/6	$N_0F_0H_0$	
34. B	R	26	--	C	26	43	6/24	$N_2F_0H_0$	2–68	7–68	5	[3] 3/60	0/5	$N_1F_0H_0$	Arterial occlusion.
	L	--	--	--			6/36	$N_2F_0H_0$	2–68	7–68	5	6/9	5/5	$N_1F_0H_0$	
35. R. B	R	44	M	C	22	42	6/12	$N_1F_1H_0$	11–64	4–68	42	6/9	42/42	$N_0F_2H_0$	Blind.

CONTROLS

36. G. B	R	42	F	C	42	56	1/60	$N_2F_2H_1$		5/68		HM	2/19	H_2	Retinal detachment.
37. B	R	72	M	C	48	64	6/12	$N_1F_0H_0$		11/64	45	4/60	0/45	H_2	
38. M. B	R	55	F	C	45	46	6/24	$N_1F_2H_0$		3/68	50	HM	14/50	H_2	
39. J. C	L	46	M	C	15	42	6/9	$N_1F_2H_0$			47	6/9	47/47	$N_0F_2H_0$	
40. E. B	R	32	F	C	4	30	6/18	$N_2F_1H_0$		1/63	23	6/24	18/23	$N_2F_2H_1$	Died.
	L	--	--	--			6/9	$N_2F_1H_0$			23	4/60	12/23	$N_2F_2H_1$	
41. H. B	R	38	M	C	25	37	6/6	$N_2F_0H_0$		7/68	49	6/5	49/49	$N_2F_1H_0$	
42. H. B	R	66	M	C	57	60	6/36	$N_1F_1H_0$		9/67	50	3/60	3/50	H_2	
	L	--	--	--			6/36	$N_1F_2H_0$			50	6/12	50/50	$N_1F_2H_0$	
43. C	L	43	M	C	8	33	HM	H_2		7/68	15	LP	9/15	H_2	Retinal detachment.
44. J. C	R	28	F	C	11	21	5/24	$N_2F_2H_1$		7/68	8	6/36	6/8	$N_2F_2H_1$	
45. J. C	L	24	F	C	3	21	6/6	$N_1F_0H_0$		6/68	24	NLP	24/24	H_2	Rubeosis secondary to glaucoma.
46. K. C	R	33	F	C	16	25	CF	$N_2F_1H_1$		3/65	50	LP	17/50	H_2	Retinal detachment, died.
	L	--	--	--			CF	$N_2F_1H_1$		3/65	50	LP	17/50	H_2	
47. F	L	47	M	C	35	41	6/60	H_2		9/63	6	HM	6/6	H_2	
48. H	L	56	M	C	35	53	6/9	$N_1F_1H_1$		7/68	20	6/60	12/20	H_2	
49. H. J	R	58	M	C	48	50	6/18	$N_2F_0H_0$		7/68	14	6/18	14/14	$N_1F_1H_1$	

See footnotes at end of table.

J. H. DOBREE—Continued

Number and patient	Eye	Age	Sex	Race	Age at onset	Age at 1st occular symptom	Visual acuity, pretreatment	Classification of retinopathy pretreatment	Date of therapy	Date of last exam	Duration of followup (months)	Visual acuity at last exam	Visual acuity retention	Classification of retinopathy at last exam	Complications and notes
50. W. J	R	63	F	C	38	61	6/9	$N_1F_2H_0$		5/68	12	6/9	12/12	$N_0F_2H_0$	
51. T. D	R	67	M	C	46	61	6/9	$N_1F_0H_0$		1/68	78	6/9	78/78	$N_1F_1H_0$	
	L	--	--	--			6/12	$N_0F_0H_0$			78	6/9	78/78	$N_2H_1H_0$	
52. C. D	R	35	M	C		35	HM	H_2		3/68	36	HM	0/36	H_2	
	L	--	--	--			6/6	$N_2F_1H_0$				HM	2/36	H_2	
53. E	R	58	M	C	42	51	6/18	$N_1F_0H_0$		7/68	78	6/36	24/78	$N_0F_2H_1$	
	L	--	--	--			6/24	$N_1F_0H_0$		7/68	78	HM	12/78	H_2	
54. T. E	R	40	M	C	9	32	6/9	$N_2F_1H_0$		7/68	96	6/60	24/96	$N_0F_2H_0$	
	L	--	--	--			6/5	$N_1F_0H_0$		7/68	96	6/9	47/96	$N_1F_2H_0$	
55. H. F	R	30	F	C	8	18	6/12	$N_1F_1H_0$		4/68	144	3/60	48/144	$N_0F_2H_0$	
	L	--	--	--			6/60	$N_1F_1H_1$			144	NLP	12/144	H_2	
56. He	R	35	M	C	2	33	6/6	$N_1F_0H_0$		5/68	16	6/6	16/16	$N_1F_0H_0$	
	L	--	--	--			6/6	$N_1F_0H_0$		5/68	16	6/6	16/16	$N_1F_0H_0$	
57. Hu	L	26	M	C	3	23	6/36	$N_0F_2H_0$		5/68	16	6/36	16/16	$N_0F_2H_0$	
58. D. I	R	44	M	C	7	37	6/5	$N_1F_0H_0$		2/68	90	6/5	90/90	$N_0F_1H_0$	
	L	--	--	--			6/5	$N_1F_0H_0$				6/5	90/90	$N_0F_0H_0$	Regression.
59. E. J	R	43	M	C	12	36	6/9	$N_2F_1H_0$		5/68	92	LP	37/92	H_2	
	L	--	--	--			6/36	H_2				LP	22/92	H_2	
60. B. J	R	34	M	C	2	32	6/5	$N_1F_2H_0$		3/65	18	6/9	14/18	$N_2F_2H_1$	Died.
61. K	L	46	M	C	22	42	6/36	$N_1F_2H_1$		4/68	46	HM	6/46	H_2	Rubeosis.
62. P. M	L	51	F	C	38	48	HM	H_2		6/68	27	HM	27/27		

63. A. M.	R	63	M	C	56	61	6/18	$N_1F_1H_0$		6/68	18	6/12	18/18	$N_1F_2H_0$	
64. S. M.	R	48	M	C	16	48	6/9	$N_1F_1H_0$		7/68	81	HM	24/81	$N_1F_2H_1$	
65. G. N.	L	69	F	C	51	66	6/9	$N_1F_0H_0$		6/67	36	6/12	24/36	$N_1F_1H_0$	
66. P.	R	61	F	C	53	58	6/18	$N_1F_0H_0$		7/68	23	6/9	23/23	$N_1F_0H_0$	
67. V. P.	R	60	F	C	50	56	6/12	$N_1F_0H_0$		4/58	40	6/36	18/40	$N_2F_1H_0$	
	L	--	--	--			6/6	$N_1F_0H_0$				6/18	18/40	$N_2F_1H_0$	
68. R.	R	57	M	C	50	50	6/36	$N_1F_0H_1$		8/68	89	LP	28/89	H_2	
	L	--	--				6/18	$N_1F_0H_1$				LP	28/89	H_2	
69. B. R.	R	45	F	C	35	39	6/6	$N_1F_0H_0$		8/68	72	6/12	48/72	$N_1F_1H_1$	
70. R. S.	R	55	F	C	50	52	6/24	$N_2F_0H_1$		1/67	36	LP	12/36	H_2	
	L	--	--	--			6/12	$N_2F_0H_0$		1/67	36	HM	18/36	H_2	Rubeosis.
71. S.	L	54	M	C	45	53	6/9	$N_1F_1H_0$			12	6/9	12/12	$N_1F_1H_0$	
72. M. T.	R	62	M	C	52	53	6/12	$N_1F_1H_0$		2/66		LP	12/90	$N_0F_2H_0$	
	L	--	--	--			HM	H_2				HM	0/0	H_2	
73. H. W.	R	68	M	C	58	54	6/18	$N_1F_1H_0$		6/68		CF	18/30	H_2	
74. W.	R	49	M	C	27	48	6/6	$N_1F_0H_0$		4/67	16	6/5	16/16	$N_1F_0H_0$	
	L	--	--	--			6/6	$N_2F_1H_0$		4/67	16	6/5	16/16	$N_2F_1H_0$	
75. Y.	L	27	F	C	2	24	6/12	$N_1F_2H_0$		6/68	30	6/9	30/30	$N_1F_2H_0$	
76. Mc.	L	46	M	C	23	45	6/6	$N_1F_0H_0$		8/68	11	6/6	11/11	$N_1F_0H_0$	
77. A. L.	R	68	M	C	67	67	6/24	$N_1F_0H_0$		6/64	37	6/18	37/37	$N_1F_1H_0$	
	L	--	--	--			6/18	BH_1		6/64	37	LP	24/37	H_2	

[1] Left eye perception of light (not a control).
[2] Right eye exudative only.
[3] Pro. 6/18 corrected.

Appendix I

(DATA FROM CHAPTER 38)

G. S. HARRIS AND P. K. RENTIERS

[Mode of therapy—PHOTOCOAGULATION]

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Date of last exam	Duration of followup (months)	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Remarks
1. Ak	R	48	M	W	26	46	20/30	$H_0N_1F_0$	4-28-66	8- 5-66	4	20/40	1	$H_0N_1F_0$	
	L	--	--	--			20/30	$H_1N_1F_0$				20/50	1	$H_1N_1F_0$	
2. An	R	63	F	W	49	60	20/30	$H_1N_2F_1$	12- 7-67	4-25-68	28	20/30	1	$H_1N_2F_1$	
	L	--	--	--			20/30	$H_1N_2F_1$		4-25-68		20/40	1	$H_1N_2F_1$	
3. Br	R	54	F	W	31	52	20/300	$H_0N_2F_2$	2-16-66	6-17-68	28	20/200	1	$H_0N_2F_2$	
4. Ca	L	47	F	W	20	46	20/50	$H_1N_2F_0$	7- 7-66	3- 8-68	21	20/200	.25	$H_2N_2F_0$	
5. De	R	65	F	W	23	56	CF-HM	H_0F_2	5-28-66	8-23-67	16	CF-HM	1		Retinal detachment.
	L	--	--	--			20/200	$H_0N_2F_2$	2-11-67		6	CF-HM	1	$H_0N_2F_2$	
6. Co	L	84	F	W	68	80	CF-HM	$H_1N_2F_0$	9-25-67	10-13-67	6	CF-HM	1	$H_1N_2F_0$	
7. Du	R	54	F	W	10	24	20/40	$H_0N_2F_1$	6- 9-66	12-11-67	18	20/50	1	$H_0N_2F_1$	
	L	--	--	--			20/20	$H_0N_2F_1$				20/20	1	$H_0N_2F_1$	
8. Fl	L	68	F	W	45	64	20/40	$H_1N_2F_2$	1966-68	1-12-68	18	20/40	1		Retinal detachment.
9. Hi	L	66	F	W	42	65	20/70	$H_1N_1F_0$			6	20/100		$H_1N_1F_0$	
10. He	L	54	M	W	52	50	CF-HM	$H_1N_2F_1$	5- 8-67	12-20-67	6	20/200	1	$H_1N_2F_1$	
11. Lo	R	57	F	W	30	55	20/200	$H_0N_1F_1$	1966(2),	8- 3-68	18	20/40	1	$H_0N_1F_1$	
	L	--	--	--			20/100	$H_0N_2F_1$	1968			CF-HM	.60	$H_0N_2F_1$	

12. Jo	L	37	M	W	12	31	20/20	$H_0N_2F_2$	3-31-66	12- 6-66	9	20/50	1	$H_0N_2F_2$	Deceased.
13. Mc	R	47	M	W	25	46	20/30	$H_1N_2F_0$	5-14-68	8- 6-68	3	20/20	1	$H_1N_2F_0$	
	L	--	--	--			20/70	$H_0N_1F_0$			3	20/30	1	$H_0N_1F_0$	
14. Mac	L	28	F	W	15	26	20/25	$H_0N_1F_0$	12-14-65	11-9-67	24	20/20	1	$H_0N_1F_0$	
15. Mag	L	52	M	W	20	45	20/60	H_1F_1	10-21-65	5-25-68	30	20/40	1	H_1F_1	Cataract.
16. Mi	L	66	F	W	29	60	20/60	H_0F_0	11- 5-66	6- 3-68	30	20/20	1	H_0F_0	
17. My	L	46	F	W	26	44	20/30	$H_1N_2F_2$	7-21-66	11- 3-66	6	20/30	1	H_1F_2	
18. Ni	R	62	F	W	55	60	20/50	$H_0N_1F_1$	8- 5-67	7-13-68	12	20/50	1	$H_0N_1F_1$	
19. Pa	R	29	F	W	9	29	20/30	$H_0N_2F_0$	7-24-67	2- 2-68	6	20/20	1	$H_0N_1F_0$	
20. Po	L	40	F	W	13	27	20/20	$H_1N_1F_2$	1966(2) 1967(2)	4-20-68	12	20/20	1	$H_0N_1F_1$	
21. Ra	L	27	M	W	12	26	20/20	H_0F_0	4-30-67	12-21-67	8	20/20	1	H_0F_0	
22. Ro	R	36	F	W	10	33	20/30	$H_0N_1F_2$	4- 6-66	2- 9-68	24	20/40	1	$H_0N_1F_2$	
	L	--	--	--			CF-HM	$H_0N_1F_0$	4-12-66	2- 9-68	24	CF-HM	1		Retinal detachment.
23. St	R	46	F	W	11	44	20/40	$H_0N_1F_0$	9-19-66	3- 3-67	6	20/25	1	$H_1N_1F_0$	
24. Sm	R	67	M	W	55	66	20/40	H_0F_0	5-12-66	11-21-66	6	20/30	1	H_0F_0	Deceased.
	L	--	--	--			20/200	H_0F_0				20/200	1	H_0F_0	
25. Sq	R	22	F	W	14	20	20/70	$H_1N_1F_0$	3-16-67	7-15-67	4	LP	.20	H_2	
	L	--	--	--			20/40	$H_1N_1F_0$				20/200	.80	$H_1N_1F_1$	
26. St	L	58	M	W	20	56	20/70	$H_1N_2F_0$	2-18-67	2-18-68	12	20/40	1	$H_1N_2F_0$	
27. Sc	R	35	F	W	10	35	20/40	$H_0N_2F_2$	1966(3)	6-28-68	30	LP	.33	$H_1N_2F_2$	
	L	--	--	--			20/25	$H_0N_2F_1$				CF-HM	.25	$H_1N_2F_2$	
28. Wi	R	56	M	W	30	55	20/60	H_0F_1	3-17-67	8-18-68	6	20/60	1	H_0F_1	
	L	--	--	--			20/70	$H_1N_2F_2$	3-16-67			CF-HM	.33	$H_1N_2F_2$	
29. Wo	R	32	F	W	25	29	20/50	$H_0N_1F_0$	6-26-66	3- 5-68	27	20/30	1	$H_0N_1F_0$	
	L	--	F	W			20/200	$H_0N_1F_0$				20/40	1	$H_0N_1F_0$	

Summary of Data

Total number of diabetic patients seen—200.

Total number of diabetic patients treated—29 up to January 1968.

Patients treated who have had previous pituitary ablative procedures—2.

Total number of treated eyes—41 up to January 1968.

Average age—50 years: 31 percent male, 69 percent female.

Average age when diabetes was diagnosed—36.3 years.

Average age of first ocular symptoms—21.4 years.

Average followup from time of treatment to date of last patient visit—1.1 year.

Average visual retention index—0.9.

Two of the patients expired. Three of the patients developed total retinal detachments during the study period—of these, two were operated upon with success. One patient developed a rapidly growing cataract which required extraction.

Using the O'Hare Classification[1], two patients showed sufficien improvement in the vitreous hemorrhage to improve their classification and three patients deteriorated to a lower stage. The remainder (24 patients) remained within the same classification bracket. One patient showed improvement in neovascularization sufficient to advance him to a higher classification and the remainder remained in the same classification bracket. Two patients developed sufficiently increased vitreous fibrosis to result to a lower bracket of classification.

Although figures show relative stability of the retinopathy, personal observation suggests that photocoagulation frequently destroys some areas of neovascularization but that other nets of vessels would not infrequently develop in other areas of the retina. Some patients required two, three, four or more sessions to keep up with the advancing pathology. The treated areas of neovascularization frequently disappeared. However, some would remain and in a few cases additional hemorrhage would occur at the treated site. Most patients had a reduction in the number of vitreous hemorrhages following treatment if this had been a problem prior to treatment. Retinitis proliferans tended to be relatively little affected by photocoagulation and some patients showed progressive vitreous fibrosis.

Observation:

All patients were asked following treatment if they were aware of scotomata produced by the photocoagulation. Interestingly enough very few were aware of the lesions produced by the treatment. Some patients had fairly large sector field defects of which they were not aware. This is probably explained by the fact that many of them

[1] O'Hare Classification, p. xxi.

suffered from retinitis proliferans with field defects prior to treatment. In addition some patients who had light treatment near the macula developed only localized scotoma without a sector defect. There is no doubt that photocoagulation benefits some patients, but another group of patients are probably not materially benefited by this treatment, and a very few patients may have been detrimentally affected by the treatment. Complications as a result of the treatment have included two retrobulbar hemorrhages. One of these in a one-eyed patient who had markedly impaired vascular supply resulted in a transient central artery occlusion with impairment of visual acuity for several days. Three cc. of 2% Xylocaine without Adrenalin is the anesthetic agent of choice. Postoperative discomfort is transient and limited to a few.

Appendix J

C. B. MORTIMER

(DATA FROM CHAPTER 40)

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Duration of follow-up (months)	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Degree of pituitary ablation	Complications
1. J. H.	OD	19	M	W	6	17	6/18	B	1961	Nil	84	6/12	1.0	BH_1		
	OS	--	--	--			6/60	$N_1F_1H_1$		LC		6/6	1.0	BH_1		
2. M. I.	OD	64	F	W	61	64	6/12	$N_1F_0H_1$	1962	LC	74	6/6	1.0	B		
	OS	--	--	--			6/6	B		Nil		6/6	1.0	B		
3. J. T.	OD	53	M	W	23	52	6/6	B	1962	Nil	72	6/6	1.0	B		
	OS	--	--	--			6/12	$N_1F_0H_1$		LC		6/6	1.0	B		
4. J. S.	OD	61	M	W	52	60	6/18	$N_1F_0H_1$	1962	LC	70	6/15	1.0	$N_1F_0H_1$		
	OS	--	--	--			6/12	BH_1		LC		6/15	0.6	BH_1		
5. S. A.	OD	59	M	W	51	58	6/18	BH_1	1963	LC	57	6/12	1.0	BH_1		
	OS	--	--	--			6/6	B		Nil		6/6	1.0	B		
6. F. H.	OD	67	M	W	64	67	6/60	$N_2F_1H_1$	1963	LC	49	LP	0	H_2		
	OS	--	--	--			6/60	$N_1F_1H_1$		2×LC		6/18	1.0	$N_1F_1H_1$		
7. P. C.	OD	22	M	W	7	19	6/60	$N_1F_1H_1$	1965	Nil	40	ILP	0	H_2		2° glaucoma; pituitary ablation reject.
	OS	--	--	--			6/120	$N_1F_1H_1$		3×LC		HM 3″	0	$N_1F_2H_1$		
8. L. A.	OD	52	F	W	50	52	6/36	$N_1F_0H_1$	1965	LC	36	6/60	0.5	$N_1F_1H_1$		
	OS	--	--	--			6/18	BH_1		LC		6/36	0.5	$N_1F_0H_1$		
9. J. D.	OD	24	M	W	6	23	6/60	$N_2F_2H_1$	1966	Nil	26	NLP	0	H_2		2° glaucoma; refused ablation.
	OS	--	--	--			6/120	$N_1F_1H_1$		LC×2		HM	0.3	$N_1F_2H_1$		
10. G. S.	OD	59	F	W	35	57	6/60	$N_1F_0H_1$	1966	LC×2	25	ALP	0.2	H_2		2° glaucoma.
	OS	--	--	--			6/60	$N_1F_1H_1$		Nil		HM	0.2	H_2		

11. A. F.	OD	56	F	--	50	55	6/36	BH_1	1966	LC	24	6/36	1.0	BH_1		
	OS	--	--	--			6/36	BH_1		LC		6/36	1.0	BH_1		
12. J. K[1]	OD	27	F	W	3	24	6/9	$N_1F_0H_1$	1966	LC	22	HM	0.1	$N_2F_1H_1$	Complete	Pituitary Ablation in 1965.
	OS	--	--	--			ILP	H_2		Nil		ILP	0	H_2		
13. M. S.	OD	28	M	W	11	27	6/60	$N_2F_1H_1$	1966	LC	19	HM	0.1	$N_2F_1H_1$		
	OS	--	--	--			HM	H_2		Nil		ILP	0	H_2		
14. A. P.	OD	26	M	W	9	24	6/12	$N_1F_0H_0$	1966	LC	19	6/15	0.5	$N_1F_1H_1$		
	OS	--	--	--			6/60	$N_1F_1H_1$		LC		HM	0	$N_1F_1H_1$		Retinal Detachment.
15. E. C.	OD	41	F	W	41	39	6/6	B	1966	Nil	18	6/6	1.0	B		
	OS	--	--	--			6/18	$N_1F_1H_1$		LC		6/7	1.0	B		Hemorrhage after LC.
16. P. C. B.	OD	31	M	W	12	27	CF 3′	$N_1F_2H_1$	1966	LC	18	ILP	0	H_2		Pituitary Ablation in 1965.
	OS	--	--	--			6/36	$N_1F_0H_1$		LC		HM	0	H_2	Complete	
17. J. S.	OD	26	M	W	8	24	6/18	$N_1F_0H_1$	1967	LC	17	6/60	0.5	$N_1F_1H_1$		Ablation reject.
	OS	--	--	--			6/12	$N_1F_1H_1$		LC		6/12	1.0	$N_1F_1H_1$		
18. B. N.	OD	58	F	W	33	54	6/120	$N_2F_2H_1$	1967	LC	16	CF 3′	0	H_2		
	OS	--	--	--			6/60	$N_1F_1H_1$		LC×2		6/36	1.0	$N_1F_1H_1$		
19. J. H.	OD	56	F	W	37	54	HM 3′	$N_2F_2H_1$	1967	LC	15	ILP	0	H_2	Complete	Ablation in 1966.
	OS	--	--	--			HM 3′	$N_2F_2H_1$		LC		ALP	0	$N_2F_2H_1$		
20. L. K.	OD	27	M	W	11	24	LP	H_2	1967	Nil	15	6/60		H_2	Complete	Ablation in 1966.
	OS	--	--	--			6/36	$N_1F_0H_1$		LC		ALP	0	H_2		
21. K. W.	OD	27	M	W	27	27	6/36	$N_1F_0H_1$	1937	LC	13	6/24	1.0	$N_1F_1H_1$		
	OS	--	--	--			6/18	$N_1F_0H_0$		LC		6/18	1.0	$N_1F_0H_1$		Ablation refusal.
22. D. H.	OD	26	M	W	9	25	6/60	$N_2F_0H_1$	1967	LC	13	CF 3′	0	$N_2F_0H_1$		
	OS	--	--	--			6/60	$N_2F_1H_1$		LC		6/60	1.0	$N_2F_1H_1$		
23. M. O.	OD	52	F	W	50	51	ILP	H_2	1967	Nil	13	ILP	0	H_2		
	OS	--	--	--			6/7	BH_1		LC		6/7	1.0	BH_1		
24. C. P.	OD	57	F	W	51	56	6/18	BH_1	1967	LC	13	6/12	1.0	BH_1		
	OS	--	--	--			ILP	H_2		Nil		ILP	0	H_2		2° Glaucoma.
25. A. B.	OD	41	M	W	18	38	ILP	H_2	1967	Nil	12	ILP	0	H_2	Incomplete.	Ablation in 1965.
	OS	--	--	--			6/6	$N_1F_0H_1$		LC		6/6	1.0	$N_1F_1H_1$		

See footnote at end of table.

333-611 O - 69 - 52

C. B. MORTIMER—Continued

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Duration of followup (months)	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Degree of pituitary ablation	Complications
26. H. W	OD	56	F	W	50	55	6/60	$N_1F_2H_1$	1967	LC×3	12	6/60	1.0	$N_1F_2H_1$		
	OS	--	--	--			6/60	$N_2F_2H_1$		LC		ALP	0	H_2		
27. A. G	OD	41	M	W	20	39	LP	$N_2F_1H_1$	1967	LC	12	ALP	0	H_2	Complete	Ablation in 1965.
	OS	--	--	--			6/18	$N_1F_0H_1$		LC×2		6/21	0.5	$N_1F_1H_1$		
28. R. D	OD	32	M	W	11	29	6/12	$N_1F_0H_1$	1967	Nil	11	6/12	1.0	$N_1F_0H_1$	Complete	Ablation in 1966.
	OS	--	--	--			6/60	$N_1F_0H_1$		LC		6/60	1.0	$N_1F_0H_1$		Field defect.
29. S. H	OD	54	M	W	50	53	6/18	BH_1	1967	LC	11	6/12	1.0	BH_1		
	OS	--	--	--			6/7	$N_1F_0H_0$		LC×2		6/7	1.0	$N_1F_0H_1$		
30. K. P	OD	49	F	W	31	47	ILP	H_2	1967	Nil	11	ILP	0	H_2		Retinal detachment.
	OS	--	--	--			6/7	BH_1		LC		6/7	1.0	BH_1		
31. E. H	OD	57	F	W	56	56	6/60	$N_1F_0H_1$	1967	LC	11	6/120	0	$N_1F_1H_1$		
	OS	--	--	--			6/12	BH_1		LC		6/9	1.0	BH_1		
32. E. W	OD	49	M	W	48	49	ILP	H_2	1967	LC	11	ILP	0	H_2		
	OS	--	--	--			6/120	$N_2F_2H_1$		LC×2		HM	0	$N_2F_2H_1$		
33. L. G	OD	27	M	W	11	26	6/60	$N_1F_0H_1$	1967	LC×2	11	6/36	1.0	$N_1F_0H_1$		
	OS	--	--	--			6/15	$N_1F_0H_1$		LC×2		6/21	0.5	$N_1F_1H_1$		
34. L. W	OD	44	M	W	20	42	6/60	$N_1F_2H_1$	1967	LC	11	6/60	1.0	$N_1F_2H_1$		
	OS	--	--	--			6/120	$N_2F_2H_1$		LC×2		CF 3′	0	$N_2F_2H_1$		Retinal detachment.
35. J. W	OD	54	M	W	26	51	CF 3′	N_2F_2H	1967	LC	10	HM	0	$N_2F_2H_1$		Retinal detach. ment.
	OS	--	--	--			6/60	$N_1F_1H_1$		LC×2		6/60	1.0	$N_1F_1H_1$		
36. A. K	OD	44	F	W	20	42	6/60	$N_2F_1H_1$	1967	LC×2	10	CF 3′	0	$N_2F_1H_1$		Heat neuritis.
	OS	--	--	--			HM 3′	$N_2F_1H_1$		LC		HM 3′	1.0	$N_2F_1H_1$		

37. B. H.	OD OS	47 --	M --	W --	22	46	6/7 6/120	BH_1 $N_1F_0H_0$	1967	LC LC	10	6/7 6/120	1.0 1.0	BH_1 $N_1F_0H_0$		
38. W. H.	OD OS	23 --	M --	W --	5	22	6/36 CF 3′	$N_1F_1H_1$ $N_1F_2H_1$	1967	LC LC×2	10	6/60 HM 3′	0.5 0	$N_1F_1H_1$ $N_1F_2H_1$		Retinal ablation. Retinal detachment.
39. W. B.	OD OS	37 --	M --	W --	19	36	6/36 6/7	BH_1 BH_1	1967	LC×2 LC	10	6/12 6/7	1.0 1.0	BH_1 BH_1		
40. H. B.	OD OS	41 --	M --	W --	18	40	6/18 6/120	$N_1F_0H_1$ $N_2F_2H_1$	1967	LC×4 LC	10	6/18 CF 3′	1.0 0	$N_1F_0H_1$ $N_2F_2H_1$		Retinal detachment.
41. L. S.	OD OS	56 --	F --	W --	32	54	6/120 CF 3′	$N_2F_1H_1$ $N_2F_2H_1$	1967	LC LC	10	CF 3′ HM	0 0	$N_2F_2H_1$ H_2		Retinal detachment.
42. J. N.	OD OS	30 --	M --	W --	9	28	6/6 6/6	$N_1F_0H_1$ $N_1F_1H_1$	1967	LC LC×2	10	6/6 6/36	1.0 0.3	$N_1F_0H_1$ $N_1F_1H_1$		
43. J. H.	OD OS	44 --	F --	W --	17	40	6/36 6/60	$N_1F_2H_1$ $N_2F_2H_1$	1967	LC LC	9	6/120 CF 3′	0 0	$N_1F_2H_1$ H_2	Complete	Ablation in 1965.
44. C. C.	OD OS	61 --	M --	W --	56	54	CF 3′ HM	$N_1F_1H_1$ $N_2F_2H_1$	1967	LC LC	9	LP LP	0 0	$N_1F_1H_1$ $N_2F_2H_1$		
45. H. Z.	OD OS	53 --	F --	W --	43	52	6/60 6/36	$N_2F_1H_1$ $N_2F_2H_1$	1967	LCX2 LC	9	6/18 6/120	1.0 0	$N_1F_1H_1$ H_2		Severe hemorrhage.
46. L. P.	OD OS	49 --	M --	W --	21	46	6/9 6/60	BH_1 $N_2F_2H_1$	1967	LCX2 LC	9	6/7 CF 3′	1.0 .1	BH_1 $N_2F_2H_1$		
47. F. H.	OD OS	57 --	M --	W --	51	56	6/36 6/24	$N_2F_1H_1$ $N_2F_2H_1$	1967	LC LC	9	6/18 6/60	1.0 .1	$N_1F_1H_1$ $N_2F_2H_1$		Heat neuritis.
48. A. L.	OD OS	32 --	F --	W --	19	30	6/7 6/18	BH_1 $N_1F_0H_0$	1967	LC LCX2	8	6/36 6/15	0 1.0	H_2 $N_1F_0H_0$		Severe hemorrhage.
49. A. L.	OD OS	34 --	M --	W --	16	31	LP 6/60	H_2 $N_2F_2H_1$	1967	LC LCX2	8	ILP 6/60	0 1.0	H_2 $N_2F_2H_1$	Complete	Ablation in 1966.
50. R. C.	OD OS	33 --	F --	W --	19	30	6/18 6/7	$N_1F_1H_1$ $N_1F_0H_1$	1967	LC LCX3	8	6/18 6/7	1.0 1.0	$N_1F_1H_1$ $N_1F_0H_1$		
51. L. R.	OD OS	42 --	M --	W --	16	40	6/12 6/60	$N_2F_1H_0$ $N_2F_1H_1$	1967	LCX2 LC	8	6/12 6/60	1.0 1.0	$N_2F_1H_0$ $N_2F_1H_1$		
52. J. P.	OD OS	30 --	M --	W --	9	29	6/7 6/36	$N_1F_0H_0$ $N_1F_0H_1$	1967	LCX2 LC	7	6/7 6/18	1.0 1.0	$N_1F_0H_0$ $N_1F_0H_1$		

C. B. MORTIMER—Continued

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Duration of followup (months)	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Degree of pituitary ablation	Complications
53.	OD	51	M	W	30	50	6/24	$N_1F_1H_1$	1967	LC	7	6/18	1.0	$N_1F_1H_1$		
	OS	--	--	--			6/18	$N_2F_1H_1$		LCX2		6/120	.3	$N_2F_2H_1$		Heat neuritis.
54.	OD	46	F	W	21	43	6/18	$N_2F_0H_1$	1967	LCX2	7	6/15	1.0	$N_1F_0H_1$		
	OS	--	--	--			6/12	$N_2F_0H_1$		LC		CF3′	0	H_2		
55.	OD	29	M	W	6	28	6/60	$N_2F_1H_1$	1967	LCX2	7	6/120	.5	$N_2F_1H_1$		
	OS	--	--	--			6/15	$N_2F_1H_0$		LCX2		6/60	.5	$N_2F_1H_1$		
56. S. K.	OD	56	F	W	49	55	6/15	$N_1F_0H_1$	1967	LC	7	6/15	1.0	$N_1F_0H_1$		
	OS	--	--	--			6/7	$N_1F_1H_1$		LCX2		6/7	1.0	$N_1F_1H_1$		
57. A. N.	OD	30	M	W	10	29	6/15	$N_1F_0H_1$	1967	LC	7	6/9	1.0	$N_1F_0H_1$		
	OS	--	--	--			6/7	$N_1F_0H_1$		LCX2		6/7	1.0	$N_1F_0H_1$		
58. G. G.	OD	34	M	W	12	32	6/6	$N_1F_0H_1$	1968	LCX2	6	6/7	0.8	$N_1F_0H_1$		
	OS	--	--	--			ALP	H_2		Nil		ALP	0	H_2		
59. C. E.	OD	46	M	W	30	44	6/60	$N_2F_1H_1$	1968	LCX2	6	6/60	1.0	$N_2F_1H_1$		
	OS	--	--	--			6/9	$N_2F_1H_1$		LC		6/9	1.0	$N_2F_1H_0$		
60. R. T.	OD	22	M	W	6	21	6/6	BH_1	1968	LC	6	6/7	0.5	BH_1		
	OS	--	--	--			ALP	H_2		Nil		ALP	0	H_2		Detached retina.
61. R. J.	OD	31	M	W	7	30	6/60	$N_1F_1H_1$	1968	LC	6	6/60	1.0	$N_1F_1H_1$		
	OS	--	--	--			6/7	$N_1F_0H_0$		LC		6/7	1.0	$N_1F_0H_0$		
62. A. P.	OD	59	M	W	54	58	6/60	$N_1F_0H_1$	1968	LC	6	6/60	1.0	$N_1F_0H_1$		
	OS	--	--	--			6/60	$N_1F_0H_0$		LC		6/60	1.0	$N_1F_0H_0$		
63. J. S.	OD	56	F	W	50	55	6/12	$N_2F_1H_1$	1968	LC	6	6/12	1.0	$N_2F_1H_1$		
	OS	--	--	--			6/60	$N_2F_2H_1$		LCX2		6/60	1.0	$N_2F_2H_1$		
64. D. D.	OD	54	M	W	48	53	6/60	BH_1	1968	LC	6	6/36	1.0	BH_1		
	OS	--	--	--			6/60	BH_1		LC		6/60	1.0	BH_1		

[1] Died January 1968.

NOTE.—1968 is date of all last examinations.

Appendix K

E. OKUN AND G. P. JOHNSTON

(DATA FROM CHAPTER 42)

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last examination	Duration of followup	Visual acuity at last examination	Visual retention index	Classification of retinopathy at last examination	Complications
1. E. A.	OD	71	F	W	51	71	CF, HM	N_2F_2	7-27-59 7-12-62	Scl. Res. Sil. Inj.	11-30-67	100 months	NLP	36/100	Det.	
	OS	--	--	--			1/400	$N_2F_2H_1$	2-19-60	PC	12- 2-66	82 months	CF 3′	82/82	$N_2F_2H_1$	
2. J. W.	OD	55	M	W	55	55	CF, HM	$N_2F_2H_1$	6-20-60 8-26-60 8-30-60 9- 2-60	(1) PC PC PC	10-22-60	4 months	HM	3/4	$N_2F_2H_1$	Vit. hem.
	OS [2]	--	--	--			LP	H_2			10-22-60		LP		H_2	
3. S. S.	OD	31	F	W	19	31	20/200	$N_2F_1H_0$	10- 4-60 10- 7-60	PC PC	10-23-61	12 months	LP		$N_2F_2H_1$	Total ret. det.
	OS [2]	--	--	--			NLP	H_1	10-23-61				LP		H_1	
4. M. K.	OD	48	F	W	34	47	20/70	$N_2F_2H_1$	10-29-60	PC	4-26-54	42 months		42/42	$N_2F_2H_1$	Vit. hem.
	OS	--	--	--		48	CF	$N_2F_2H_1$	9-23-60	Scl. Bkl.	4-27-64	43 months	HM	7/43	$N_2F_2H_1$	Vit. hem.
5. P. B.	OD	48	M	W	28	48	20/30	$N_1F_0H_0$	12-13-60	PC	2- 8-61	2 months	20/30	2/2	$N_1F_0H_0$	
	OS	--	--	--			20/40	$N_2F_0H_1$	11- 9-60	PC	2- 8-61	3 months	20/70		$N_2F_0H_0$	

See footnotes at end of table.

E. OKUN AND G. P. JOHNSTON—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last examination	Duration of followup	Visual acuity at last examination	Visual retention index	Classification of retinopathy at last examination	Complications
6. E. H.	OD	29	M	W	9	29	20/15	$N_2F_1H_1$	11-15-60 2- 4-61 4-14-61 8-15-61 2-26-62 3-26-62 4-20-62 4-26-62	PC PC PC PC PC PC PC PC	4-15-68	89 months	HM	37/89	H_2	Vit. hem.
	OS	30	M	W	9	29	20/25	$N_2F_2H_1$	8-15-61 12- 5-61 2-26-62 4-20-62 4-26-62 10- 1-62 11-21-62 8-27-63	PC PC PC PC PC PC PC PC	4-15-68	80 months	CF 18″			
7. H. C.	OD	54	F	W	34		20/25	$N_2F_2H_1$	12-30-60	PC	8-10-68	92 months	HM 4′		H_1	
	OS	--	--	--			HM	H_2	1-18-61	PC	8- 9-67	79 months	20/200	79/79	N_2F_1	
8. W. C.	OD	54	M	W	47	47	LP	$N_2F_2H_1$	1-27-61 2- 2-61	PC	3-31-65	46 months	20/300	46/46	$N_2F_2H_1$	
	OS [2]	--	--	--			HM	$N_2F_1H_1$			3-31-65		20/400		$N_2F_1H_1$	
9. J. D.	OD	27	F	W	22	26	20/70	$N_2F_2H_1$	3-27-61	PC	2-19-66	58 months	20/70	58/58	$N_2F_2H_0$	
	OS	--	--	--			20/20	$N_2F_2H_0$	3-29-61	PC	2-19-66	do	20/50	58/58	$N_2F_2H_1$	
10. G. B.	OD	24	M	W	16	24	20/30	$N_2F_1H_1$	2- 9-62 5- 2-62 8-29-62 9-29-62	PC PC PC PC	5-20-68	75 months	NLP	48/75	$N_2F_2H_2$	Rubeosis iridis.
	OS [2]	--	--	--			CF 2′	$N_2F_0H_1$	12-12-61 12-29-62 7-30-64 12-11-64 1- 2-65 4-15-65	PC PC PC PC PC PC	5-20-68	79 months	LP	40/79	$N_2F_2H_1$	

11. L. B.	OD	42	M	W	12	39	20/30−2	$N_2F_2H_1$	2-22-62 3-31-62	PC Scl. Bkl.	12- 3-66	58 months	20/200	58/58	$N_2F_2H_1$	
	OS	--	--	--			CF 6′	$N_2F_2H_1$	2-23-62	Scl. Bkl.	12- 3-66	do	LP	10/58	$N_2F_2H_1$	
12. B.	OS	65	M	W			20/200	$N_2F_1H_1$	4-25-62	PC	3-30-65	35 months	CF	35/35	$N_2F_2H_1$	
	OD [2]	--	--	--			CF	$N_2F_2H_1$			3-30-65		HM		$N_2F_2H_1$	
13. M. H.	OD	72	F	W	71	69	20/300	$N_2F_2H_1$	6- 1-62	PC						
	OS [2]	--	--	--			20/300	$N_2F_2H_1$	6- 1-62							
14. C. B.	OD	57	M	W	49	55	CF 3′	$N_2F_0H_1$	10- 6-62	PC	3-10-66	42 months	20/800 or CF 6′.	42/42	$N_2F_1H_0$	
	OS [2]	--	--	--			20/25	$N_1F_0H_0$			3-10-66		20/20		$N_1F_0H_0$	
15. H. H.	OS	73	M	W			20/200	$N_2F_1H_1$	10- 4-62	PC	6- 5-67	56 months	20/25+	56/56		
	OD [2]	--	--	--												
16. L.	OD	54	F	W			CF	$N_2F_2H_1$	11-15-62	PC	2- 5-63	3 months	LP		$N_2F_2H_1$ (R)	Det. ret. 1 month after PC.
	OS [2]	--	--	--			LP	$N_2F_2H_2$			2- 5-63		LP		$N_2F_2H_2$	
17. D. W.	OS	25	M	W	12	24	20/25	$N_2F_2H_1$	12- 8-62 12-31-62 1- 1-63	PC PC PC	9-12-67	57 months	HM	0/57	$N_2F_2H_1$	
	OD [2]	--	--	--			HM	$N_2F_2H_1$			9-12-67		NLP		$N_2F_2H_1$	
18. G. V.	OD	40	M	W	15		20/100	$N_2F_1H_1$	12-19-62 12-13-62	PC Scl. Bkl.	1-16-63	1 month	20/40		$N_2F_1H_1$	
	OS [2]	--	--	--			HM	$N_2F_2H_1$			1-16-63		20/400		$N_2F_2H_1$	
19. A. R.	OS	53	M	W	31	52	20/400	$N_2F_1H_1$ (R)	12-18-62 12-24-62 5-27-68	Scl. Bkl. PC PC	5-26-68	65 months	20/400	65/65	$N_2F_2H_1$	
	OD [2]	--	--	--			20/50	$N_2F_1H_1$			5-26-68		20/200		$N_2F_2H_0$	
20. L.S.	OD	38	M	W	26	38	HM, CF	$N_2F_2H_1$	1- 9-63	Scl. Bkl.	4- 8-63	3 months	CF 3′	3/3	$N_2F_2H_1$	
	OS	--	--	--			20/100	$N_2F_1H_0$	1- 9-63	PC	4- 8-63	do	CF 3′	3/3	$N_2F_2H_1$	
21. L.D.	OD	55	F	W	45		20/200	$N_2F_1H_0$	1-23-64	PC	4- 3-65	15 months	20/200	15/15	$N_2F_1H_0$	
	OS [2]	--	--	--			Amaurosis	$N_2F_2H_2$			4- 3-65		Amaurosis		$N_2F_2H_2$	
22. J.R.	OS	52	M	W	40		CF	$N_2F_0H_1$	3-10-63	PC	5-23-66	38 months	20/300	38/38	$N_2F_1H_0$	
	OD [2]	--	--	--			20/30	$N_2F_1H_0$			5-23-66		20/300		$N_2F_1H_0$	
23. A.M.	OD	23	M	W	5	19	20/200+2	$N_2F_1H_0$	5-25-63 12- 5-63	PC PC	8- 3-68	63 months	20/30	63/63	$N_2F_2H_0$	
	OS [2]	--	--	--			HM	$N_2F_2H_2$			8- 3-68		HM		$N_2F_2H_2$	

See footnotes at end of table.

E. OKUN AND G. P. JOHNSTON—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last examination	Duration of followup	Visual acuity at last examination	Visual retention index	Classification of retinopathy at last examination	Complications
24. E.F.	OD	62	F	W			20/30	$N_1F_0H_1$	6- 7-63 7-25-63 3-24-64	PC PC PC	2-27-65	20 months	20/30	20/20	$N_1F_0H_0$	
	OS	--	--	--			20/50	$N_1F_0H_1$	11-25-63 3-25-64	PC PC	2-27-65	15 months	Amaurosis	7/15	$N_2F_1H_1$	
25. M.C.	OD	56	F	W	39	56	20/20	$N_1F_0H_0$	8- 5-63 2-11-65 12-28-65 3-27-66	PC PC PC PC	8-22-68	60 months	20/70	60/60	$N_2F_2H_0$	
	OS	--	--	--			20/70	$N_2F_1H_1$	6-12-63	PC	8-22-68	62 months	HM	19/62	$N_2F_2H_0$	
26. M.R.	OD	30	F	W	5		20/30	$N_2F_1H_0$	10-18-63	PC	10- 8-64	12 months	20/25	12/12	$N_2F_1H_0$	
	OS	--	--	--			20/50	$N_2F_1H_0$	7- 8-63	PC	10- 8-64	15 months	20/50	15/15	$N_2F_1H_0$	
27. E. F.	OS	49	F	W	34	47	20/100	$N_2F_1H_2$	7-24-63 2- 4-64	PC Scl. Bkl.	7-15-64	12 months	Amaurosis	12/2	$N_2F_2H_0$	
	OD [2]	--	--	--			CF	$N_2F_1H_2$			7-15-64		20/200		$N_2F_1H_0$	
28. E. H.	OD	45	F	W	16	44	20/70	$N_2F_1H_1$	8- 2-63	Scl. Bkl. and PC.	5-27-68	57 months	HM	7/57	H_2	
	OS	--	--	--			20/70	$N_2F_1H_1$	8-14-63 11-23-63 3-12-64 3-20-65	PC PC PC PC	5-27-68	do	HM	27/57	$N_2F_2H_1$ (R_3)	
29. P.	OS	29	F	W	10		HM	$N_2F_0H_2$	8-30-63	PC	6- 1-64	10 months	HM	0	$N_2F_0H_2$	
	OD [2]	--	--	--			20/30	$N_1F_0H_0$			6- 1-64		20/40		$N_1F_0H_0$	
30. M. D.	OD	67	F	W	65	66	20/100+1	$N_2F_0H_1$	9- 5-63 1-17-64 3-28-64	PC PC PC	11- 7-64	14 months	20/200	14/14	$N_2F_0H_0$	
	OS	--	--	--			20/200	$N_2F_1H_0$	3-26-64	PC	11- 7-64	8 months		8/8	$N_2F_1H_0$	

31. L. T.	OD	53	M	W	32	46	20/30	$N_2F_0H_0$	9/27-63	PC	12- 3-64	15 months	20/30	15/15	$N_2F_0H_1$	One interval vit. hem.
	OS [2]	--	--	--			CF	$N_2F_2H_0$ (R)			12- 3-64		HM		$N_2F_2H_1$ (R)	
32. M. S.	OS	25	F	W	10		20/30	$N_2F_0H_0$	10-28-63 11-15-63 2-21-64 3- 8-65	PC PC PC Stalk sec.	7-29-68	57 months	20/25+3	57/57	$N_2F_0H_0$	
	OD [2]	--	--	--			20/400	$N_2F_2H_1$			7-29-68		CF		$N_2F_2H_0$ (R_3)	
33. M. G.	OD	59	F	W	44	59	20/40	$N_1F_0H_0$	11-13-63	PC	8-10-64	9 months	20/50	9/9	$N_1F_0H_0$	
	OS [2]	--	--	--			20/40	$N_1F_0H_0$			8-10-64		20/25		$N_1F_0H_0$	
34. D. B.	OD	23	F	W	5	22	20/30	$N_2F_0H_0$	11-16-63	PC	3-10-65	16 months	20/40	16/16	$N_2F_0H_0$	
	OS [2]	--	--	--			HM	$N_2F_0H_2$			3-10-65		20/70		$N_2F_1H_0$	
35. C. J.	OS	57	F	W	56	57	20/40	$N_1F_0H_0$	11-26-68	PC	1-31-66	26 months	20/70	26/26	$N_1F_0H_0$	
	OD [2]	--	--	--			20/100	$N_1F_0H_0$			1-31-66		20/100		$N_1F_0H_0$	
36. G. L.	OD	65	F	W	64	65	20/20	$N_1F_0H_0$	12- 6-63 5-28-64	PC PC	11-27-67	47 months	20/30+2	47/47	$N_1F_0H_0$	
	OS [2]	--	--	--			20/20	$N_1F_0H_0$			11-27-67		20/30		$N_1F_0H_0$	
37. P. H.	OD	32	F	W	19		20/30	$N_2F_1H_1$	12-20-63	PC	1-10-67	37 months	CF 5′	37/37	$N_2F_2H_0$	
	OS	--	--	--			20/200	$N_2F_2H_0$	4-24-65	PC	1-10-67	21 months	20/60	21/21	$N_2F_1H_0$	
38. E. G.	OD	65	F	W	42		20/70	$N_1F_0H_0$	1- 9-64	PC	3- 5-65	14 months	20/300	14/14	$N_1F_0H_0$	Maculopathy.
	OS [2]	--	--	--			20/40	$N_1F_0H_0$			3- 5-65		20/30		$N_1F_0H_0$	
39. M. S.	OS	62	F	W	55	62	20/70	N_2F_0	1-10-64 12-26-64	PC PC	7-30-68	54 months	20/30+	54/54	$N_2F_0H_0$	
	OD [2]	--	--	--			HM 18″	H_2			7-30-68		HM		H_2	
40. F. G.	OD	56	F	W	54	54	20/100+	$N_1F_0H_1$	1-14-64 2-24-64 10-25-66	PC PC PC	3-18-68	50 months	20/70	50/50	$N_1F_0H_1$	
	OS	--	-	--			20/70	$N_2F_0H_1$	3-20-65 6-17-66 4-25-67 3-19-68	PC PC PC PC	3-18-68	36 months	20/70	36/36	$N_1F_0H_1$	
41. F. N.	OD	38	F	W	18		20/40	$N_1F_0H_0$	1-13-64	PC (14 times)	6-24-67	41 months	CF 4′	41/41	$N_2F_1H_1$	
	OS [2]	--	--	--			LP	$N_2F_2H_1$			12- 6-65		Enucleation.			

See footnotes at end of table.

E. OKUN AND G. P. JOHNSTON—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last examination	Duration of followup	Visual acuity at last examination	Visual retention index	Classification of retinopathy at last examination	Complications
42. C. D.	OD	61	M	W			20/25	$N_1F_0H_1$	1-16-64	PC	10-13-65	21 months		21/21	$N_1F_0H_0$	
	OS [2]	--	--	--			CF	$N_2F_1H_2$			10-13-65		LP		$N_2F_0H_2$	
43. K. S.	OD	44	F	W	24	43	CF 2′-3′	$N_1F_0H_0$	2- 1-64 9-18-64 1- 8-65	PC PC PC	5-27-68	51 months	CF 2′	51/51	$N_2F_0H_0$	Edema and hem. in mac. area.
	OS [2]	--	--	--			20/25	$N_1F_0H_0$			5-27-65		$N_1F_0H_0$			
44. M. P.	OS	39	F	W	21	38	20/70	$N_2F_2H_1$	2-18-64 3-24-64 8- 9-64 3-15-66	PC PC PC Scl. Bkl.	10- 9-67	44 months	CF	42/44	$N_2F_2H_1$	
	OD [2]	--	--	--			HM	$N_2F_2H_1$			10- 9-67		Amaurosis		H_2	
45. E. R.	OD	62	F	W			CF 6′	$N_2F_0H_1$	3-26-64	PC	1-18-66	22 months	CF 4′	22/22	$N_2F_0H_1$	
	OS	--	--	--			CF 3′	$N_2F_0H_1$	2-18-64	PC	1-18-66	do	CF 2′-3′	22/22	$N_2F_0H_1$	
46. R. A.	OD	50	M	W	35	50	20/70	$N_2F_0H_0$	2-21-64	PC	7-15-68	53 months	20/30+2	53/53	$N_2F_0H_0$	
	OS	51	--	--			20/50	$N_2F_0H_0$	11-19-64 5-14-65	PC Scl. Bkl.	7-15-68	44 months	20/400	44/44	$N_2F_1H_0$	
47. G. C.	OS	60	M	W	34		HM	$N_2F_2H_1$	2-21-64	PC	3-11-64	1 month	HM	0	$N_2F_2H_1$	
	OD [3]	--	--	--												
48. W. F.	OS	54	M	W	51	52	20/40	$N_1F_0H_0$	3-11-64 5-29-64 8- 3-64	PC PC PC	8-15-67	41 months	Can read	41/41	$N_2F_1H_0$	
	OD [2]	--	--	--			20/300	$N_2F_2H_1$			8-15-67		do		$N_2F_2H_0$	
49. E. D.	OD	59	M	W	46	58	20/50	$N_2F_0H_0$	3-24-65 4-27-65	PC PC	9- 5-67	30 months	20/40	30/30	$N_2F_0H_0$	
	OS	--	--	--			20/70	$N_2F_0H_0$	3-14-64 4-25-64 11-24-64 12-27-64 4-27-65	PC PC PC PC PC	9- 5-67	42 months	20/200	24/42	$N_2F_0H_0$	

50. M. W.	OD	59	F	W	46	54	CF 54″	$N_2F_1H_2$	12–26–64	PC	7–29–68	43 months	20/30	43/43	$N_2F_1H_0$	
	OS	--	--	--			CF 6′	$N_2F_1H_2$	3–26–64	PC	7–29–68	52 months	CF 2′	52/52	$N_2F_1H_0$	
									5–14–64	PC						
									7–24–64	PC						
									12–26–64	PC						
									4– 5–66	Scl. Bkl.						
51. I. K.	OD	59	F	W	42	58	20/40	$N_2F_0H_0$	3–31–64	PC	3–20–68	48 months	HM	41/48	$N_2F_2H_1$–H_2.	
									2–10–65	PC			barely.			
	OS	--	--	--			CF	$N_2F_2H_1$	2–10–65	(4)	3–20–68	37 months	Amaurosis	7/37	$N_2F_2H_1$	
52. L. W.	OD	56	M	W	17	55	20/400	$N_2F_1H_0$	5–12–64	PC	8– 9–65	15 months	20/300	15/15	$N_2F_1H_0$	
									9– 9–64	PC						
	OS	--	--	--			CF 6′	$N_2F_0H_0$	4–15–64	PC	8– 9–65	16 months	20/300	16/16	$N_2F_0H_0$	
									11– 5–64	PC						
53. J. Y.	OD	64	M	W			20/200	$N_2F_0H_1$	4–17–64	PC	5–17–67	37 months	20/300	37/37	$N_2F_0H_0$	
	OS [2]	--	--	--			HM	H_2			5–17–67		20/200		$N_2F_1H_1$	
54. E. H.	OD	38	F	W	26		20/20	$N_1F_0H_0$	4–21–64	PC	11–28–66		20/30		$N_2F_0H_0$	
									1–27–65	PC						
	OS	--	--	--			20/60	$N_2F_0H_1$	4–17–64	PC	11–28–66		20/100		$N_2F_1H_0$ (R).	
									7– 9–64	PC						
									7–28–64	PC						
55. N. W.	OD	61	F	W	(5)		10/400	$N_2F_1H_1$	4–21–64	PC	3–26–65	11 months	15/400	11/11	$N_2F_1H_1$	
	OS [2]	--	--	--			HM	$N_2F_2H_1$			3–26–65		CF		$N_2F_2H_0$	
56. S.	OD	67	M	W			20/400	$N_2F_0H_1$	8– 8–64	PC	1–23–65	5 months	20/100	5/5	$N_2F_0H_0$	
	OS	--	--	--			20/400	$N_2F_1H_1$	4–18–64	PC	1–23–65	9 months	20/100	9/9	$N_2F_1H_0$	
57. J. B.	OD	55	M	W	54	54	20/70	$N_1F_1H_0$	4–29–64	PC	8–22–68	52 months	20/50	52/52	H_1	
	OS	--	--	--			CF	$N_1F_0H_1$	3–17–67	PC	8–22–68	17 months	20/100	17/17	$N_2F_1H_1$	
									8–23–68	PC						
58. M. D.	OS	65	F	W	46	62	20/200	$N_1F_0H_1$	5–12–64	PC	3– 5–68	46 months	HM	38/46		
									3–11–66	PC						
									8– 2–66	(6)						
	OD [2]	--	--	--			NLP [7]		11– 5–66	(6)	3– 5–68		Amauro-sis.			
59. H. S.	OS	63	F	W	47	62	20/30	$N_2F_0H_0$	5–28–64	PC	7–17–68	50 months	CF 18″	50/50	$N_2F_2H_1$	Rec. vit. hem.
									12– 4–64	PC						
									2–13–64	PC						
									6–12–65	PC						
									9–29–65	PC						
	OD [2]	--	--	--			CF 9′	$N_2F_0H_2$			7–17–68		HM		D	

See footnotes at end of table.

E. OKUN AND G. P. JOHNSTON—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last examination	Duration of followup	Visual acuity at last examination	Visual retention index	Classification of retinopathy at last examination	Complications
60. F. V.	OD	31	M	W	11	23	20/20	$N_1F_0H_0$	5-29-64 4-29-66	PC PC	8-19-68	51 months	20/20+3	51/51	$N_2F_0H_0$	
	OS	--	--	--			20/20	$N_2F_0H_1$	1-16-68 2- 8-68	PC PC	8-19-68	7 months	CF 4′	7/7	$N_2F_2H_1$	
61. S. A.	OS	43	F	W	18	41	20/25	$N_2F_0H_0$	6- 4-64 9-22-64 12-11-65 4-13-66 6-20-66 3- 1-67 7-19-67 10-25-67 7-24-68	PC PC PC PC PC PC PC PC PC	7-24-68	49 months	20/50	49/49		Rec. hems.
	OD [2]	--	--	--			20/25	$N_1F_0H_0$			7-24-68		HM			
62. F. B.	OD	59	M	W	44		20/70	$N_2F_0H_0$	3- 1-65	PC	1-26-66	10 months	HM, CF 1′	/10	H_1–H_2	
	OS	--	--	--			CF 6′	$N_2F_0H_2$	6- 8-64	PC	1-26-66	19 months	CF 2′–3′	19/19	H_1	
63. R. M.	OD	31	M	W	14	29	20/40	$N_1F_0H_1$	6-11-64	PC	3- 2-68	45 months	20/30	45/45	$A=H_0$	
	OS [2]	--	--	--			20/200	$N_2F_1H_0$			3- 2-68		20/70+1		$N_2F_1H_0$	
64. E. B.	OD	58	M	W	51	52	20/200	$N_1F_0H_0$	6-20-64	PC	3-16-68	45 months	20/70	45/45	$N_1F_0H_0$	
	OS [2]	--	--	--			20/200	$N_1F_0H_0$			3-16-68		20/70		$N_1F_0H_0$	
65. N. L.	OD	28	M	W	18		20/200	$N_1F_0H_0$	6-25-64	PC	8-17-67	26 months	([3])	26/26		
	OS [2]	--	--	--			20/70	$N_1F_0H_0$			8-17-67		([3])			
66. C. F.	OD	33	M	W	15	32	20/80	$N_1F_0H_0$	7- 3-64	PC	5-11-68	46 months	20/40+2	46/46	$N_2F_0H_0$	
	OS [2]	--	--	--			20/20	$N_1F_0H_0$			5-11-68		20/20		NF_0H_0	

67. C.R.	OD	36	F	W			20/70	$N_2F_0H_0$	7- 3-64	PC	5-25-68	46 months	20/40+2	46/46	$N_2F_1H_0$
	OS	--	--	--			20/70	$N_2F_0H_0$	7- 5-64	PC	5-25-68	do	20/40-3	46/46	$N_2F_0H_0$
									10-15-64	PC					
									1- 9-65	PC					
									11-13-65	PC					
									10-15-66	PC					
									11- 5-66	PC					
68. C.D.	OD	26	F	W	11	26	20/50	$N_2F_0H_1$	7-13-64	PC	2-28-66	19 months	20/100	19/19	$N_2F_0H_1$
	OS	--	--	--			20/40	$N_2F_0H_1$	7-10-64	PC	2-28-66	do	20/200	19/19	$N_2F_0H_1$
									9-30-64	PC					
									12-14-64	PC					
69. C.B.	OD	61	F	W			20/200	$N_2F_1H_1$	7-13-64	PC	12- 3-65	17 months	HM 2'	/17	$N_2F_2H_0$
	OS [2]	--	--	--											
70. J. S.	OS	28	M	W	13	28	20/70	$N_2F_0H_0$	7-21-64	PC	2-21-68	43 months	20/30	43/43	$N_2F_1H_0$
									11-13-64	PC					
	OD [2]	--	--	--			20/25	$N_1F_0H_0$			2-21-68		20/200		$N_2F_2H_1$
71. B.	OD	50	F	W			CF	$N_2F_0H_1$	8- 3-64	PC	3- 1-67	31 months	NLP	0	N_2F_2
	OS	--	--	--			CF	$N_2F_0H_0$	9-14-64	PC	3- 1-67	30 months	NLP		N_2F_2
72. S. H.	OD	63	M	W	43	60	20/50-	$N_2F_0H_1$	8- 4-64	PC	1-19-65	5 months	CF 3'	/5	$N_2F_0H_0$
	OS [2]	--	--	--			20/25	$N_1F_0H_0$			1-19-65		20/30		$N_1F_0H_0$
73. J. B.	OD	47	M	W			20/50	$N_2F_0H_1$	8-10-64	PC	11-27-64	3 months	CF	3/3	$N_2F_0H_1$
	OS	--	--	--			CF	$N_2F_0H_1$	9-21-64	PC	11-27-64	2 months	CF	2/2	$N_2F_0H_1$
74. R. C.	OD	36	M	W	17		20/50	$N_2F_0H_1$	10-12-64	PC	1-11-67	27 months	HM 3'	/27	H_2
	OS	--	--	--			CF	$N_2F_0H_1$	8-10-64	PC	1-11-67	29 months	LP		H_2
75. C. M.	OD	27	M	W	16		CF 1'	$N_2F_2H_1$	8-23-64	PC	1-22-68	41 months	Amaurosis	2/41	$N_2F_2H_2$
	OS	--	--	--			CF 15'	$N_2F_1H_1$	10- 7-64	PC	1-22-68	39 months	HM	29/39	$N_2F_2H_1$ (R_4)
76. M. M.	OS	49	F	W	44	46	20/300	$N_2F_1H_0$	8-26-64	PC	5-27-68	45 months	20/200	45/45	$N_2F_1H_0$
	OD [2]	--	--	--			20/40	$N_1F_0H_0$			5-27-68		20/25+2		$N_2F_1H_0$
77. E. L.	OD	84	F	W	69		20/300	$N_2F_0H_0$	8-31-64	PC	2-18-66	18 months	20/100	18/18	$N_2F_1H_1$
	OS [2]	--	--	--			CF 2'	$N_2F_1H_1$			2-18-66		HM		$N_2F_1H_1$
78. V. C.	OD	37	M	W	11	37		$N_2F_0H_1$	10-29-64	PC	2-19-65	4 months	20/30	4/4	$N_2F_0H_1$
									12- 3-64	PC					
	OS	--	--	--			CF 2'	$N_2F_2H_1$ (R)	10-28-64	PC	2-19-65	do	HM	/4	$N_2F_2H_1$

See footnotes at end of table.

E. OKUN AND G. P. JOHNSTON—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last examination	Duration of followup	Visual acuity at last examination	Visual retention index	Classification of retinopathy at last examination	Complications
79. R. J	OS	52	M	W	32	52	20/400	NFH	11- 4-64 11- 7-64 12- 5-64	PC PC PC	7-16-67	32 months	CF	32/32		
	OD [2]	--	--	--			20/400	$N_2F_1H_1$	3- 6-65 5- 1-65	PC PC	7-17-67		HM			
80. H. Z	OS	55	M	W	31	53	20/25	$N_1F_0H_1$	11-11-64 3-20-65	PC PC	5-22-65	6 months	20/40	6/6	$N_1F_0H_1$	Subhyaloid hem. from disc.
	OD [2]	--	--	--			20/25	$N_1F_0H_0$			5-22-65		20/30+		$N_1F_0H_0$	
81. C. S	OS	27	F	W	12	27	20/25	$N_2F_0H_0$	11-12-64 1- 5-65 2-24-65 3-20-65 3- 6-65 4- 3-65 5- 1-65 5-22-65	PC PC PC PC PC PC PC PC	7-28-68	44 months	20/25	44/44	$N_2F_0H_0$	
	OD [2]	--	--	--			HM, CF 6′	$N_2F_0H_2$ (R)			7-29-68		20/50+1		$N_2F_2H_0$	
82. J.S	OS	55	M	W	52	55	CF 5′	$N_2F_2H_1$	11-13-64	PC	7-23-68	44 months	CF	44/44	$N_2F_2H_1$ (R_1)	
	OD [2]	--	--	--			CF 6″	$N_2F_2H_1$ (R_3)			7-23-68		HM		H_1-H_2	
83. R.T	OS	38	F	W	18	36	20/25	N_2F_1-F_2	11-13-64	PC	6-24-68	43 months	20/30+2	43/43	N_2F_2	
	OD [2]	--	--	--			20/400	N_2F_2			6-24-68		20/30+3		N_2F_2	
84. E.D	OD	30	M	W	12		20/70+	$N_2F_0H_0$	12-31-64	PC	1-19-65	1 month	20/40+	1/1	$N_2F_0H_0$	
	OS	--	--	--			20/200	$N_2F_0H_1$	11-20-64	PC	1-19-65	2 months	20/100	2/2	$N_2F_0H_1$	
85. J.O	OS	52	M	W	34		20/60	$N_2F_2H_1$	11-19-64 8-15-65	PC PC	8-10-68	45 months	HM	17/45	$N_2F_2H_1$	Membrane formation.
	OD [2]	--	--	--			20/50	$N_2F_2H_1$			10-24-66		LP		[9]	

86. F. H.	OS	33	M	W	13	33	20/25	NFH	11–20–64 2–27–65 10–25–65 2– 5–68	PC PC PC (6)	7–29–68		20/20		
	OD [2]	--	--	--											
87. M. R.	OD	51	F	W	24		CF 2′	$N_2F_0H_1$	11–23–64	PC	4–27–65	5 months	CF 2′	5/5	N_2F_0–F_1 H_1–H_2
	OS [2]	--	--	--			20/30	$N_2F_2H_0$ (R_3)			4–27–65		20/30		$N_2F_2H_0$
88. H. C.	OD	47	M	W	28	47	20/25	$N_2F_0H_1$	11–23–64 11–10–67 2–19–68	PC PC PC	7–17–68	44 months	20/30+3	44/44	$N_2F_1H_1$
	OS	50	--	--	28	47		$N_2F_1H_1$	11– 7–67 1–30–68	PC PC	7–17–68	8 months	20/50–2	8/8	$N_2F_1H_1$
89. C. H.	OD	38	M	W	18	38	20/200	$N_2F_2H_0$	11– 2–64	PC	5–16–68	42 months	Enucleated.	5/42	
									5–16–68	Enucleated.					
	OS [2]	--	--	--			20/100	$N_2F_1H_0$			5–15–68		NLP		H_2
90. O. S.	OD	68	F	W	51		20/200	$N_2F_0H_1$	11–30–64	PC	4–13–66	17 months	20/200	17/17	$N_2F_0H_0$
	OS	--	--	--			20/400	$N_2F_0H_1$	4– 2–66	PC	4–13–66	11 days	20/400		$N_2F_0H_0$
91. A. R.	OD	29	F	W	8	26	20/30	N_2F_2	12– 3–64	PC	4– 1–68	40 months	20/25–3	40/40	$N_2F_1H_0$
	OS [2]	--	--	--			HM	$N_2F_2H_2$			4– 1–68		20/100		$N_2F_2H_1$
92. E. L.	OD	31	M	W	14		20/30	$N_2F_0H_0$	12– 3–64	PC	8–23–65	8 months	20/300	8/8	N_2F_1–F_2H_1
	OS [2]	--	--	--			20/40	$N_2F_0H_0$			8–23–65		20/100		$N_2F_0H_1$
93. S. H.	OS	62	M	W	44	62	20/20	$N_1F_0H_0$	12– 4–64	PC	10–23–67	34 months	20/20	34/34	$N_1F_0H_0$
	OD [2]	--	--	--			20/25+1	$N_1F_0H_0$			10–23–67		20/25		$N_2F_0H_0$
94. C. L.	OS	57	F	W	47	46	20/40	$N_1F_0H_0$	1– 6–65	PC	6–24–68	41 months	20/50	41/41	$N_1F_0H_0$
	OD [2]	--	--	--			20/40	$N_1F_0H_0$			6–24–68		20/50		$N_2F_0H_0$
95. L. B.	OS	45	M	W	30		20/400	$N_1F_0H_0$	1– 6–65	PC	12– 3–66	23 months	20/400	23/23	$N_1F_0H_0$
	OD [2]	--	--	--			20/70	$N_1F_0H_0$			12– 3–66		20/70		$N_2F_2H_0$ (R_3)
96. J. T.	OD	39	F	W	11	38	20/20	$N_1F_0H_0$	1– 7–65	PC	12–10–66	23 months	20/25	23/23	$N_1F_0H_0$
	OS [2]	--	--	--			20/25	B			12–10–66		20/30		B
97. O. G.	OS	56	M	W	49	55	CF	$N_2F_0H_1$	1–13–65 7– 1–65 2–24–66	PC PC PC	4–26–67	27 months		/27	
	OD [2]	--	--	--			20/40	$N_2F_0H_1$			2–24–66		CF 3′		

See footnotes at end of table.

E. OKUN AND G. P. JOHNSTON—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last examination	Duration of followup	Visual acuity at last examination	Visual retention index	Classification of retinopathy at last examination	Complications
98. J. M.	OD	37	F	W	19	37	20/40	$N_2F_1H_1$	1-14-65	PC	2-20-67	25 months	20/30+2	25/25	$N_2F_1N_1$	Vit. hem.
	OS [2]	--	--	--	----	----	20/30	$N_1F_0H_0$	----	----	2-20-67	----	20/25+1	----	$N_2F_0H_0$	
99. J. R.	OS	50	M	W	35	49	20/80	$N_2F_1H_0$	1-15-65	PC	5- 3-67	28 months	HM	24/28	$N_2F_2H_1$ (R_1)	
									4- 5-66	Scl. Bkl.						
	OD [2]	--	--	--	----	----	20/20	$N_1F_0H_0$	----	----	5- 3-67	----	HM	----	$N_2F_2H_1$	
100. L. S.	OS	63	F	W	30	64	20/40	$N_2F_1H_1$	1-20-65	PC	5- 6-68	40 months	20/30	40/40	$N_2F_2H_0$ (R_1)	
	OD [2]	--	--	--	----	----	20/20	$N_1F_0H_0$	----	----	5- 6-68	----	20/25	----	$N_2F_0H_0$	
101. R. S.	OD	23	M	W	5	22	20/100	$N_2F_0H_0$	1-27-65	PC	10-15-65	9 months	Enucleation.	5/9	----	
									5-17-65	PC						
	OS [2]	--	--	--	----	----	20/70-1	$N_2F_0H_0$	----	----	1-15-67	----	CF	----	$N_2F_1H_1$	
102. L. K.	OD	66	M	W	51	----	CF 4′	$N_2F_1H_0$	2- 8-65	PC	11- 4-65	9 months	CF 2′-3′	9/9	$N_2F_0H_0$	
	OS [2]	----	----	----	----	----	20/400	$N_2F_1H_0$	----	----	11- 4-65	----	CF 2′-3′	----	$N_2F_0H_1$	
103. R. D.	OD	43	F	W	42	43	HM, CF	$N_2F_2H_1$	12- 8-64	Scl. Bkl.	5- 1-65	5 months	LP	3/5	$N_2F_2H_1$	
	OS	----	----	----	----	----	20/70	$N_2F_2H_1$	12-18-64	PC	5- 1-65	----do----	CF	5/5	$N_2F_2H_1$	
									2-17-65	PC						
104. C. A.	OS	58	F	W	39	57	20/50+1	$N_2F_0H_1$	2- 9-65	PC	6-12-67	28 months	NLP	----	----	
	OD [2]	----	----	----	----	----	HM	$N_2F_0H_2$	----	----	6-12-67	----	HM	----	----	
105. W. W.	OD	39	M	W	21	37	20/400	$N_2F_2H_1$	2-11-65	PC	----	----	----	----	----	----
								(R)	3-27-65	PC						
	OS	--	----	----	----	----	CF 3′	$N_2F_2H_1$	2-10-65	PC	----	----	----	----	----	
								(R)	3-28-65	PC						
106. H. T.	OD	43	F	W	26	40	20/80	$N_2F_0H_1$	12-24-65	PC	7-15-68	31 months	CF 6″	31/31	$N_2F_2H_1$	Recurrent vit. hem.
									9-15-66	Scl. Bkl.						
	OS	44	--	--	----	----	CF 1′	$N_2F_2H_1$	3-30-67	Scl. Bkl.	7-15-68	16 months	LP	4/16	H_2	
								(R_3)								
107. E. G.	OD	46	M	W	31	----	20/40	$N_2F_0H_1$	2-11-65	PC	6-13-66	16 months	20/200	16/16	$N_2F_0H_0$	
	OS [2]	--	--	--	----	----	20/40	$N_2F_0H_0$	4- 2-66	----	6-13-66	----	20/25	----	$N_2F_0H_1$	

108. C. D	OD	59	F	W			20/50	$N_1F_0H_1$	3- 8-65	PC	2- 9-66	11 months	20/50	11/11	$N_2F_0H_1$	
	OS	--	--	--			20/200	$N_1F_0H_1$	2-15-65	PC	2- 9-66	12 months	20/60	12/12	$N_2F_0H_1$	
109. M. S	OS	24	M	W	4	20	20/30+	$N_2F_0H_1$	2-17-65	PC	7- 1-68	41 months	20/25	41/41	$N_2F_0H_0$	
	OD [2]	--	--	--			20/30+	$N_1F_0H_0$			7- 1-68		20/25		$N_2F_0H_0$	
110. A. R	OD	47	M	W	41	47	20/50	$N_1F_0H_0$	2-23-65	PC	10-15-66	20 months	20/25	20/20	$N_1F_0H_0$	
	OS [2]	--	--	--			20/70+1	$N_1F_0H_0$			10-15-66		20/25		$N_1F_0H_0$	
111. G. C	OD	23	M	W	6	20	20/25—	$N_2F_0H_0$	11-22-67	PC	11-22-67	0	20/25—			
	OS	20	--	--			20/25+	$N_2F_0H_0$	2-25-65	PC	11-22-67	33 months	20/25+	33/33	$N_2F_0H_0$	
									11-22-67	PC						
112. I. G	OD	68	F	W			20/100	N_2F_0	2-25-62	PC	1- 6-65	35 months		35/35	N_2F_0	
	OS	--	--	--			20/40	N_2F_0	3- 2-62	PC	1- 6-65	34 months	20/50	34/34	N_2F_0	
113. M. H	OD	68	F	W	52	68	CF 3′	$N_1F_0H_1$	11-20-63	PC	6-18-68	55 months	20/200	55/55	$N_1F_0H_0$	
									1-23-64	PC						
									3-13-64	PC						
	OS [2]	--	--	--			20/300	$N_1F_0H_0$			6-18-68		20/200+		$N_1F_0H_0$	
114. J. R	OD	38	M	W	17		20/20	$N_2F_0H_0$	12-13-63	PC	2- 7-67	38 months	20/200	38/38		
									2- 8-64	PC [10]						
	OS	--	--	--			20/50	$N_2F_1H_0$	2- 8-64	PC	5-14-64	Enuc				
115. C. C	OS	62	F	W	32	61	20/200	$N_2F_1H_1$	4- 7-64	PC	8-15-66	28 months	CF 2′	28/28	H_1–H_2	
	OD [2]	--					CF	$N_2F_1H_0$			8-15-66		CF			
116. F. G	OD	48	M	W	49	41	20/200	$N_2F_1H_1$	10-17-64	PC	10-23-67	36 months	LP	31/36		Rubeosis.
	OS	--					20/300	$N_2F_0H_1$	4- 7-64	PC	10-23-67	42 months	20/400	42/42		
117. R. P	OS	59	F	W	41		20/200+1	$N_2F_0H_1$	2- 1-65	PC	11- 5-66	21 months	20/200	21/21	$N_2F_0H_1$	
	OD [2]	--					20/40	$N_2F_0H_0$			11- 5-66		20/30		$N_2F_0H_0$	
118. A. S	OD	75	F	W	45	73	20/80	$N_2F_1H_1$	3-1-65	PC	7-10-67	28 months	NLP	/28		Rubeosis—absolute gl., optic atrophy.
									3-20-65							
	OS [2]	--	--	--			20/50+	$N_2F_1H_1$			7-10-67		CF			
119. C. B	OD	58	F	W	38	53	20/40	$N_2F_1H_0$	6-18-65	PC	12-27-67	30 months	CF 2′	30/30	$N_2F_2H_1$	
									9-15-67	PC						
	OS	--	--	--			20/25	$N_1F_0H_0$	3- 5-65	PC	12-27-67	33 months	20/80	33/33	$N_2F_2H_0$	

See footnotes at end of table.

333-611 O - 69 - 53

E. OKUN AND G. P. JOHNSTON—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last examination	Duration of followup	Visual acuity at last examination	Visual retention index	Classification of retinopathy at last examination	Complications
120. M. B.	OS	52	F	W	19	51	20/25	$N_2F_1H_1$	3-11-65 6-21-66 7- 8-66 8-24-66 10-25-66 10- 3-67	PC PC PC PC PC PC	4-29-68	37 months	HM-CF	31/37	$N_2F_2H_1$	Vit. hem.
	OD [2]	--	--	--			20/50+				4-29-68		20/40		$N_2F_2H_0$	
121. N. H.	OD	32	F	W	10	30	20/50	$N_2F_0H_1$	2-23-66	Scl. Bkl.	6- 4-68	28 months	20/100+2	28/28	$N_1F_1H_1$	
	OS	31		--			20/25	$N_2F_1H_0$	3-23-65	PC	6- 4-68	39 months	20/25+1	39/39	$N_2F_1H_0$	
122. A. M.	OD	71	F	W	37		20/200	$N_2F_0H_1$	3-15-67	PC	5-10-67	2 months	20/200	2/2	$N_2F_0H_1$	
	OS	69	--	--			20/60	$N_2F_0H_0$	3-29-65	PC	5-10-67	26 months	HM	2/6	$N_2F_0H_1$	
123. F. L.	OS	60	M	W	59	59	20/200	$N_1F_0H_1$	4- 5-65	PC	6- 8-68	38 months	20/40	38/38	$N_1F_0H_0$	
	OD [2]	--	--	--			20/70	$N_1F_0H_0$			6- 8-68		20/30+2		$N_2F_0H_1$	
124. R. S.	OD	43	F	W	30	43	20/25	$N_1F_0H_0$	4- 8-65	PC	7-29-68	39 months	20/30-2	39/39	$N_2F_1H_0$-(H_1)	
									2- 1-68	PC						
	OS [2]	--	--	--			20/25	$N_1F_0H_0$			7-29-68		20/25		$N_2F_0H_0$	
125. B.	OD	72	F	W			20/30	$N_2F_1H_0$	4- 8-65	PC	5-28-68	37 months	20/400	37/37	H_2	
	OS [2]	--	--	--			20/30	$N_2F_1H_0$			5-28-65		20/40+		$N_2F_1H_0$	
126. M. B.	OD	41	F	W	24	41	20/20	$N_2F_1H_1$	4-11-65 5-23-65 7-24-65 11- 6-65 2-19-66 10-21-66	PC PC PC PC PC PC	7- 6-67	27 months	20/300	27/27	$N_2F_1H_0$ $-H_1$	
	OS [2]	--	--	--			20/80	$N_2F_2H_2$			7- 6-67		HM		H_2	

127. R. S.	OD	51	F	W	31	46	20/40	$N_2F_2H_1$	2-16-66	PC	8- 3-68	30 months	20/30	30/30	$N_2F_1H_0$	Recurrent vit. hem.
	OS	--	--	--		50	20/50	$N_2F_2H_1$	4-21-65 8-31-65 10-27-65 2-16-66 6-21-66 10- 6-67	PC PC PC PC PC PC	8- 3-68	40 months	20/100	40/40	$N_2F_1H_1$	
128. B. T.	OS	47	F	W	39		20/15	$N_1F_0H_0$	4-23-65	PC	5-17-67	25 months	20/30-1	25/25	$N_2F_0H_0$	
	OD [2]	--	--	--			20/200	$N_2F_2H_1$ (R)			5-17-67		20/70		$N_2F_2H_1$	
129. A. C.	OD	59	F	W	41		20/400	$N_2F_1H_1$	5- 6-65	PC	9-14-66	17 months	CF	17/17	$N_2F_2H_1$	
	OS [2]	--	--	--			20/200	$N_2F_0H_1$			9-14-66		20/200		$N_2F_2H_1$	
130. C. S.	OD	73	F	W	63	69	20/400	$N_2F_0H_1$	2- 1-68	PC	5- 1-68	3 months	20/400	3/3	$N_2F_0H_0$	
	OS	69	--	--			20/60	$N_2F_0H_0$	5- 7-65 1-25-66	PC PC	5- 1-68	36 months	20/100 -1	36/36	$N_2F_0H_0$	
131. L. R.	OS	54	F	W	27	51	20/300	$N_2F_2H_0$	5- 7-65 4-18-67	PC PC	5-27-68	36 months	20/100-1	36/36	$N_2F_1H_0$	
132. J. C.	OD	66	M	W	62	64	HM	N_2F_2	5-25-67	Scl. Bkl.	7-15-68	14 months	HM	0/0	$N_2F_2H_1$ (R_4)	
	OS	64	--	--			20/70	$N_2F_1H_1$	5-20-65	PC	7-15-68	38 months	HM	19/38	H_2	Vit. hem. source: tips of ret. proliferans.
133. E. H.	OD	68	F	W			20/400									
	OS [2]	--	--	--												
134. C. P.	OD	29	M	W	12	27	CF 2'-3'	$N_2F_2H_1$	7-25-67	PC	5-27-68	10 months	HM	2/10	$N_2F_2H_1$	
	OS	27	--	--			20/300	$N_2F_0H_0$ $-H_1$	5-25-65 7- 9-65 12-14-65 12- 6-66 12-26-67	PC PC PC PC PC	5-27-68	36 months	20/400	36/36	$N_2F_2H_1$	
135. A. O.	OD	65	F	W	36		20/200	$N_2F_0H_1$	5-27-65	PC	6- 7-65	1 month	20/200+	1/1	$N_2F_0H_1$	
	OS [2]	--	--	--			CF 1'	$N_1F_0H_0$			6- 7-65		HM 54"		$N_1F_0H_0$	
136. G. A.	OD	55	F	W	44		20/50	$N_1F_0H_0$	6-17-65	PC	6-14-67	24 months	20/70	24/24		
	OS [2]	--	--	--			20/30	$N_1F_0H_0$			6-14-67		20/30		$N_2F_0H_0$	
137. M. A.	OS	51	F	W	44	51	20/50	$N_1F_0H_0$	6-25-65	PC	7- 1-68	37 months	20/40+2	37/37	$N_1F_0H_0$	
	OD [2]	--	--	--			20/40	$N_1F_0H_0$			7- 1-68		20/40+2		$N_1F_0H_0$	

See footnotes at end of table.

E. OKUN AND G. P. JOHNSTON—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last examination	Duration of followup	Visual acuity at last examination	Visual retention index	Classification of retinopathy at last examination	Complications
138. E. R.	OD	57	F	W	39	57	20/200−1	$N_2F_1H_1$	7- 8-65 5-16-66	PC PC	5- 6-68	34 months	CF 2′-3′	34/34	$N_2F_1H_1$	
	OS	59	--	--	--------	--------	20/70−	$N_2F_2H_0$ (R_3).	7-20-67	Scl. Bkl.	5- 6-68	10 months	20/70	10/10	$N_2F_2H_0$	
139. L. D.	OS	67	F	W	37	55	20/300	$N_2F_1H_1$	6- 9-65 8-10-65	PC PC	8- 9-65	2 months	20/300	2/2	$N_2F_1H_1$	
	OD [2]	--	--	--	--------	--------	20/300	$N_2F_1H_1$	----------	----------	8- 9-65	----------	20/200	----------	$N_2F_1H_1$	
140. L. B.	OD	30	M	W	14	--------	20/50+2	$N_2F_0H_1$	8-16-65	PC	1-19-66	5 months	20/400	5/5	$N_2F_0H_1$	
	OS [2]	--	--	--	--------	--------	20/400	$N_2F_0H_1$	----------	----------	1-19-66	----------	20/70−2	----------	N_2F_1	
141. M.C.	OS	27	F	W	14	--------	20/300	$N_2F_0H_0$	9- 8-65	PC	5-10-67	20 months	LP	----------	$N_2F_2H_1$	
	OD [2]	--	--	--	--------	--------	20/70+	$N_2F_0H_1$	----------	----------	5-10-67	----------	NLP	----------	$N_2F_2H_1$–$H_2(R_3)$	
142. B.K.	OD	32	F	W	20	32	20/100	$N_2F_0H_1$	10-12-65	PC	7-22-68	33 months	LP	16/33	$N_2F_2H_1$–H_2	
	OS [2]	--	--	--	--------	--------	20/70− 20/50+	$N_2F_1H_2$	----------	----------	7-22-68	----------	Amaurosis.	----------	----------	
143. E.A.	OD	69	F	W	57	66	20/40+3	$N_2F_1H_1$	1-23-68	PC	7-15-68	6 months	20/40+	6/6	$N_2F_0H_0$	
	OS	67	--	--	--------	--------	20/100+2	$N_2F_0H_0$	10-19-65 1-29-66	PC PC	7-15-68	33 months	20/50−2	33/33	$N_2F_0H_0$	
144. F.K.	OS	56	M	W	55	56	CF 3′	$N_2F_0H_1$	10-26-65	PC	10-24-66	12 months	NLP	1/12	----------	Rubeosis and massive hem.
	OD [2]	--	--	--	--------	--------	CF 6′	$N_2F_0H_1$	----------	----------	10-24-66	----------	HM	----------	$N_2F_2H_1$ (R_2)	
145. M. M.	OD	53	F	W	37	--------	20/40−2	$N_2F_0H_1$	10-30-65	PC	7- 9-66	9 months	20/60−2	9/9	$N_2F_0H_1$	
	OS [2]	--	--	--	--------	--------	20/40−2	$N_2F_0H_0$	----------	----------	7- 9-66	----------	20/70	----------	$N_2F_0H_1$	
146. A. B.	OD	43	M	W	21	--------	20/50−1	$N_2F_0H_1$	11- 4-65	PC	2-26-66	3 months	20/60+1	3/3	$N_2F_0H_1$	
	OS [2]	--	--	--	--------	--------	20/50−1	$N_2F_0H_1$	--------	------	2-26-66	----------	20/400	----------	--------	

147. H. K.	OD	63	M	W	62	63	20/40	$N_2F_1H_1$	11- 5-65	PC	4- 3 67	17 months	20/40	17/17	$N_2F_0H_0$	
	OS [2]	--	--	--			20/40	$N_2F_0H_1$			4- 3-67		20/30		$N_2F_0H_0$	
148. J. S.	OS	48	M	W	16	40	20/30	$N_2F_1H_1$	12- 9-65 1-22-66 7-16-66 10-29-66 3-13-68	PC PC PC PC PC	6- 8-68	30 months	20/25	30/30	$N_1F_2H_0$	Recurrent hems.
	OD [2]	--		--			HM, CF	H_2			6- 8-68		LP		H_2	
149. I.W.	OS	52	F	W	50		CF 6′	$N_2F_2H_1$ (R)	1-10-66	PC	4- 6-66	3 months	HM	0		
	OD [2]	--	--	--			3/200	$N_2F_2H_1$			4-10-66		NLP			
150. L.P.	OS	51	F	W	35	47	20/100	$N_2F_2H_1$ (R)	1- 6-66	PC	6- 3-67	17 months	20/300	17/17	N_2F_1	
	OD [2]	--	--	--			20/50	$N_1F_0H_0$			6- 3-67		20/20		N_2F_1	
151. E.N.	OS	29	F	W	7	27	20/30	$N_2F_1H_1$	1-11-66	PC	6-12-67	17 months	20/20−3	17/17	$N_2F_1H_0$−H_1	
	OD [2]	--	--	--			20/20	$N_2F_0H_1$			6-12-67		20/25+		$N_2F_1H_0$	
152. R.H.	OD	43	M	W			CF 6′	$N_2F_1H_1$	11-23-65 1-18-66	PC PC	2-26-66	3 months	CF 6′	3/3	$N_2F_1H_1$	
	OS [2]	--	--	--			20/100	$N_2F_1H_1$			1-16-66		CF 3′			
153. M. P.	OD	59	F	W	39		20/25	$N_1F_0H_0$	11-27-65	PC	12-21-65	1 month	20/25	1/1	$N_1F_0H_0$	
	OS [2]	--	--				20/20	$N_1F_0H_0$			12-21-65		20/25	1/1	$N_1F_0H_0$	
154. M. D.	OD	68	F	W	(11)	51	20/400	$N_2F_1H_1$	1-18-66	PC	9- 7-67	20 months	20/80	20/20	$N_1F_0H_0$	
	OS [2]	--	--	--												
155. E. F.	OD	49	F	N	34	49	20/30	$N_2F_1H_1$	1-28-66 6-29-67	PC Scl. Bkl.	5-20-68	28 months	HM	15/28	$N_2F_2H_1$ (R_4)	
	OS [2]	--	--	--			CF 6′	$N_2F_2H_1$ (R_1)			5-20-68		20/400		$N_2F_2H_1$ (R_3)	
156. I. S.	OD	69	F	W	57	65	20/100	$N_2F_0H_0$	1-28-66	PC	3- 9-66	20 months	20/200	2/2	$N_2F_0H_0$	
	OS [2]	--	--	--			20/50	$N_2F_0H_0$			3- 9-66		20/50		$N_2F_0H_0$	
157. D.F.	OD	58	F	W	33		20/400	$N_1F_0H_1$	2- 1-66	PC	6-26-68	28 months	20/200+1	28/28	$N_2F_0H_0$	
	OS	61	--	--			20/30−2	$N_2F_0H_1$	3- 5-68 5-28-68 6-27-68	PC PC PC	6-26-68	3 months	20/50	3/3	$N_2F_0H_1$	Sub-ret. bleed—residual.
158. M.F.	OD	61	F	W	53	61	20/30+	$N_2F_0H_1$	2- 2-66 4-27-66	PC PC	7-11-68	29 months	20/25−	29/29	$N_2F_0H_0$	
	OS [2]	--	--	--			20/25	$N_2F_0H_1$			7-11-68		20/30−2		$N_2F_1H_0$	

See footnotes at end of table.

E. OKUN AND G. P. JOHNSTON—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last examination	Duration of followup	Visual acuity at last examination	Visual retention index	Classification of retinopathy at last examination	Complications
159. F.B.	OD	45	M	W	21	45	20/20	$N_2F_0H_0$	2-22-66 7- 4-66	PC PC	6-24-68	28 months	20/25+2	28/28	$N_1F_0H_0$	
	OS	45	M	W	21	45	20/30	$N_2F_1H_0$	8-24-65 2- 1-66	PC PC	6-24-68	34 months	20/25−3	34/34	$N_2F_1H_0$	Hem.
160. J.H.	OS	39	M	W	25	37	20/200−1	$N_2F_1-F_2H_1$	2- 8-66	PC		None				
	OD [2]	--	--	--							2- 8-66		LP			
161. M.O.	OS	63	F	W	51		20/30+		2- 8-66	PC	8-15-66	6 months	20/25	6/6		Ret. tear with vit. hem.
	OD [2]	--	--	--			20/20				8-15-66		20/25			
162. W.S.	OS	43	M	W	15	43	20/25	$N_2F_0H_1$	2-17-66 8-11-66 9-13-66	PC PC PC	6-24-68	28 months	20/25	28/28	$N_2F_0H_0$	Pre-hyaloid, hem.
	OD [2]	--	--	--			20/50	$N_2F_2H_1$ (R_1)			6-24-68		LP			
163. G.O.	OD	48	M	W	28	47	20/70	$N_1F_0H_0$	3- 3-66	PC	8-10-66	5 months	CF	5/5		
	OS [2]	--	--	--			20/20	$N_1F_0H_0$			3- 2-66					
164. I.W.	OD	50	F	W	30	50	20/30	$N_2F_0H_1$	3-10-66 8-16-66 11-28-67	PC PC PC	7- 1-68	28 months	20/70	28/28	$N_2F_1H_1$	Hem.
	OS [2]	--	--	--			20/20	N_2F_0			7- 1-68		HM		H_2	
165. H. B.	OD	50	M	W	35	50	20/70	$N_2F_2H_1$	3-15-66	PC	11- 7-66	8 months	20/400	8/8	$N_2F_2H_1$	
	OS [2]	--	--	--			20/300	$N_2F_2H_1$			11- 7-66		CF 1′		$N_2F_2H_1$	
166. D. K.	OS	41	F	W	24		20/50+	N_1-N_2, $F_1F_2H_1$	4- 1-66	PC	5-10-67	13 months	20/40	13/13	$N_2F_2H_0$	
	OD [2]	--	--	--			20/25−1	$N_2F_1H_0$			5-10-67		20/40+1		$N_2F_2H_1$	
167. K. K.	OS	28	M	W	13	28	20/50−1	$N_2F_0H_1$	5 -10-66	PC	8- 1-66	3 months	20/30−3	3/3	$N_2F_1H_0$	
	OD [2]	--	--	--			20/70	$N_2F_0H_1$			8- 1-66		20/25		$N_2F_0H_0$	

168. J. H.	OS	42	M	W	12	40	CF 2′–3′		5–12–66 6– 2–66 6–28–66 12– 8–66 7–11–67	PC PC PC (12) (13)	7–17–68	26 months	CF	26/26	$N_2F_2H_1$ (R_2)	Vit. hem.
	OD [2]	--	--	--							12–13–65		Amaurosis.			
169. R. G.	OD	31	M	W	15	31	CF	$N_2F_0H_0$	7–19–66 3–13–68	Scl. Bkl. (6)	8–12–68	25 months	NLP	4/25	$N_2F_1H_1$	
	OS	--	--	--			20/30	$N_2F_0H_0$	5–17–66 3–13–68	PC (6)	8–12–68	27 months	20/40+3	27/27	$N_2F_1H_1$	
170. M. M.	OD	--	F	W	(14)		20/40–3	$N_2F_0H_1$	5–18–66	PC	4–19–67	11 months	20/400	11/11	$N_2F_0H_1$	
	OS [2]	--	--	--			20/50	$N_2F_0H_1$			4–19–67		20/30+2		$N_2F_0H_1$	
171. V. J.	OS	67	F	W	49	31	20/400	$N_2F_1H_0$ (R_1)	5–24–66	PC	11–14–66	6 months	CF 3′	6/6	$N_2F_1H_1$ (R_1)	
	OD [2]	--	--	--			20/70+3	$N_2F_1H_0$			11–14–66		20/200		$N_2F_1H_0$ (R_1)	
172. M. P.	OD	72	F	W	57		20/70–	$N_2F_0H_0$	6– 6–66	PC	4–26–67	10 months	20/70–1	10/10	$N_2F_0H_0$	
	OS [2]	--	--	--			20/200	$N_2F_0H_0$			4–26–67		20/100		$N_2F_0H_1$	
173. M. H.	OD	70	F	W	68	70	20/70–2	$N_2F_0H_1$	6–28–66	PC	6–19–67	12 months	20/60	12/12		
	OS [2]	--	--	--			20/40	$N_2F_1H_1$			7–15–68		CF		$N_2F_2H_1$	
174. D. S.	OS	36	M	W	10	36	20/30+1	$N_2F_0H_0$	6–30–66 10–13–66 2–20–68	PC PC PC	7–15–68	25 months	20/25	25/25	$N_2F_1H_0$	Small hems. off PC scar.
	OD [2]	--	--	--			20/40	$N_2F_1H_1$			7–15–68		CF		$N_2F_2H_1$	
175. J. O.	OD	24	M	W	2	22	20/25	$N_2F_0H_0$	7– 4–66 8– 9–66	PC PC	4–13–68	21 months	HM, CF	16/21	$N_2F_2H_1$	
	OS [2]	--	--	--			20/400	$N_2F_0H_1$–H_2			4–13–68		20/400		$N_2F_2H_1$–H_2	
176. E. C.	OD	59	F	W	49		CF 2′	$N_2F_0H_1$	8– 6–66	PC	6–14–67	10 months	CF 3″	10/10	$N_2F_1H_0$	
	OS [2]	--	--	--			20/70	$N_2F_0H_0$			6–14–67		20/70–1		$N_2F_0H_0$	
177. D. R.	OD	28	F	W	6	28	20/400	$N_2F_2H_1$	3–14–67	Scl. Bkl.	3–10–68	12 months	20/200	12/12	$N_2F_2H_1$	
	OS	--	--	--			20/200	$N_2F_2H_1$	9– 8–66	PC	3–10–68	18 months	20/200	18/18	$N_2F_2H_0$	
178. M. A.	OD	50	F	W	35	50	CF	$N_2F_0H_1$	9–13–66	PC	8–19–68	23 months	20/200	23/23	$N_2F_0H_0$	
	OS	--	--	--			20/200	NFH	9–13–66	PC	8–19–68	do	20/200	23/23		

See footnotes at end of table.

E. OKUN AND G. P. JOHNSTON—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last examination	Duration of followup	Visual acuity at last examination	Visual retention index	Classification of retinopathy at last examination	Complications
179. L. S.	OS	42	M	W	15	41	20/40	$N_1F_0H_1$	10–25–66 11–26–66 3– 9–67 3–29–67 6– 8–67 6–11–68 7– 2–68 7–25–68	PC PC PC PC PC PC PC PC	7–25–68	21 months	20/20	21/21	$N_2F_1H_0$	
	OD [2]	--	--	--			20/30+2	N_2F_1			6–10–68		20/20		$N_2F_0H_0$	
180. B. W.	OS	48	F	W	43		20/400	$N_2F_0H_0$	10–26–66	PC	12– 1–67	26 months	Poor LP	/26		
	OD [2]	--	--	--			20/300 20/200				12– 1–67		20/300			
181. M. P.	OD	69	F	W	38	58	20/40	$N_2F_0H_1$	12–15–66 3– 2–67 11–20–67	PC PC PC	7–23–68	19 months	CF 2′	19/19	$N_2F_2H_1$ (R_3)	
	OS [2]	--	--	--			HM				7–23–68		LP			
182. C. B.	OD	48	F	W	32	43	20/50−3	N_2F_1	12–20–66 1–24–67 2–16–67 11–14–67 8–13–68	PC PC PC PC PC	8–12–68	20 months	20/40	20/20	$N_2F_1H_1$	Recurrent vit. hem.
	OS [2]	--	--	--			20/50−1	$N_2F_2H_0$			8–12–68		20/200		$N_2F_2H_1$	
183. K. M.	OD	73	M	W	65	71	20/70	$N_2F_1H_1$	1–21–67 3– 2–67 6–11–68	PC PC PC	7–15–68	18 months	20/70	18/18	$N_2F_1H_1$	
	OS [2]	--	--	--												
184. P. B.	OS	27	F	W	7	27	20/30	$N_2F_0H_1$	1–12–67	PC	6–10–68	17 months	20/25+2	17/17	$N_1F_0H_0$	
	OD [2]	--	--	--			20/200	N_2F_1–F_2H_1			6–10–68		CF 1′–2′		N_2F_1–F_2H_1	

185. R. W.	OS	39	M	W	23	36	20/300	$N_2F_1H_1$	1-12-67 5-13-68	PC PC	6- 1-68	17 months	10/400	17/17	$N_2F_1H_0$	
	OD [2]	--	--	-	- - - -	- - - - -	20/200	N_1–N_2 F_0H_0	- - - - - - - - - -	- - - - - - - - - -	6- 1-68	- - - - - - -	CF 6″	- - - - - - - - - -	- - - - - - - - - -	
186. A. G.	OS	66	F	W	57	- - - -	20/400	$N_2F_1H_0$	1-16-67	PC	8- 2-67	7 months	CF 4′	7/7	$N_2F_1H_1$	
	OD [2]	--	-	--	- - - -	- - - -	20/400	$N_2F_0H_0$	- - - - - - - - - -	- - - - - - - - - -	8- 2-67	- - - - - - -	CF 4′	- - - - - - - - - -	$N_2F_0H_1$	
187. J. M.	OD	58	M	W	37	57	20/40	$N_2F_0H_1$	1-17-67	PC	7-22-68	18 months	20/25	18/18	$N_1F_0H_0$	
	OS	--	--	--	- - - -	- - -	20/40	$N_2F_0H_1$	5-23-68	PC	7-22-68	2 months	20/70	2/2	$N_1F_0H_0$	
188. J. K.	OS	42	M	W	27	41	20/30+	$N_2F_0H_1$	1-19-67 4-25-67 6- 8-67 7-11-67 10-24-67	PC PC PC PC PC	5-29-68	16 months	20/70+2	16/16	$N_2F_2H_1$	Vit. hem.
	OD [2]	--	--	--	-- - - -	- - - - -	LP	H_2	- - - - - - - - - -	- - - - - - - - - -	5-29-68	- - - - - - -	LP	- - - - - - - - - -	- - - - - - - - - -	
189. A. H.	OD	23	F	W	12	23	20/25	$N_2F_0H_1$	11-11-66 2- 2-67	(15) PC	7-31-68	20 months	20/30	20/20	$N_1F_2H_1$	Vit. hem.
	OS			-	- - - - -	- - -	CF 1′–2′	$N_2F_1H_1$–H_2.	- - - - - - - - - -	- - - - - - - - - -	7-31-68	do	20/40+3	20/20	$N_1F_2H_0$	Vit. hem.
190. F. S.	OS	64	M	W	60	- - - - -	20/50−	$N_2F_1H_1$	2-14-67	PC	7-12-67	5 months	20/200	5/5	$N_2F_1H_1$ (R).	
	OD [2]		--	--	-- - - - -	- - - -	20/100+1	$N_2F_0H_0$	- - - - - - - - - -	- - - - - - - - - -	7-12-67	- - - - - - -	20/200	- - - - - - - - - -	$N_2F_0O_0$	
191. R. C.	OS	52	M	W	35	50	20/25	$N_2F_1H_1$ –H_2	2-23-67 3-30-67 6- 8-67 1-17-68 2-22-68 4-16-68 8-27-68	PC PC PC PC PC PC PC	8-26-68	18 months	20/40+2	18/18	$N_2F_1H_1$	
	OD [2]	--	--	--	- - - - - - - -	- - - - -	CF	$N_2F_2H_2$	- - - - - - - - - -	- - - - - - - - - -	8-26-68	- - - - - - -	CF	- - - - - - - - - -	$N_2F_2H_2$	
192. H. H.	OD	60	M	W	- - - - - - - -	- - - - - - -	20/70	$N_2F_1H_1$	3-10-67	PC	8-19-67	17 months	20/400	17/17	$N_2F_1H_1$	
	OS [2]	--	-	--	- - - - - - - -	- - - - - - -	20/25	$N_2F_0H_0$	- - - - - - - - - -	- - - - - - - - - -	8-19-68	- - - - - - -	20/25	- - - - - - - - - -	$N_2F_1H_0$	
193. V. D.	OS	56	F	W	42	55	20/300	$N_2F_0H_0$	4- 6-67	PC	6- 6-68	14 months	20/300	14/14	$N_2F_0H_0$	
	OD [2]	--	--	-	- - - - - - - -	- - - - - - -	20/70	$N_2F_0H_0$	- - - - - - - - - -	- - - - - - - - - -	6- 6-68	- - - - - - -	20/300	- - - - - - - - - -	$N_2F_0H_0$	
194. K. O.	OD	30	M	W	14	30	20/40	$N_2F_1H_0$	4-10-67	PC	7-17-68	15 months	20/400	15/15	$N_2F_2H_1$	
	OS	--	--	--	- - - - - - - -	- - - - - - -	20/25	$N_2F_0H_0$	10-12-67 3-14-68	PC PC	7-17-68	9 months	20/40	9/9	$N_2F_1H_0$	

See footnotes at end of table.

E. OKUN AND G. P. JOHNSTON—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last examination	Duration of followup	Visual acuity at last examination	Visual retention index	Classification of retinopathy at last examination	Complications
195. J. E.	OD	54	F	W	33	51	CF 4′	N_2F_1–F_2H_1	10–12–67 7–25–68	PC PC	8–27–68	10 months	20/300	10/10	$N_1F_1H_0$	
	OS	--	--	--			20/300	$N_2F_0H_1$	4–11–67	PC	8–27–68	16 months	20/70	16/16	N_1F_1H	
196. H. N.	OS	58	F	W	40	52	20/200	$N_2F_0H_1$	4–27–67 6–18–68	PC PC	7–31–68	15 months	CF 1′	15/15	$N_2F_1H_1$	
	OD [2]	--	--	--			CF 2′	$N_2F_2H_1$			7–31–68				$N_2F_2H_0$	
197. R. H.	OD	42	M	W	1	41	20/40+2 20/200−1	$N_2F_1H_1$	4–27–67 10–19–67	PC PC	4– 3–68	12 months	CF 6″	12/12	H_2	
	OS [2]	--	--	--			HM	H_2			4– 3–68					
198. F. F.	OS	59	F	W	40		20/30−1	$N_2F_0H_1$	4–28–67	PC	5–24–67	1 month	20/30	1/1	$N_2F_0H_0$	
	OD [2]	--	--	--			20/50−1	$N_1F_0H_0$			5–24–67		20/30+1		$N_1F_0H_1$	
199. R. H.	OD	56	F	W	38	56	20/40	$N_2F_0H_1$	4–28–67 7–20–67	PC PC	8–14–68	16 months	CF 1′	16/16	$N_2F_1H_1$	
	OS [2]	--	--	--			CF 2′	H_2			8–14–68		20/200		$N_2F_1H_1$	
200. E. R.	OD	50	M	W	40	48	20/40	$N_2F_1H_1$	5– 9–67	PC	9– 9–67	4 months	20/50+1	4/4	$N_1F_0H_0$	
	OS	--	--	--			20/40	$N_1F_1H_1$	9– 9–67 9–11–67	PC PC	9–16–67	None				
201. P. M.	OD	26	F	W	8	26	20/25	$N_2F_0H_1$	5–23–67 10–23–67 10–10–68 5–21–68	PC PC PC PC	6–10–68	13 months	20/20	13/13	$N_2F_0H_0$	
	OS [2]	--	--	--			20/20	N_1–$N_2F_0H_1$			6–10–68		20/25		$N_2F_0H_0$	
202. D. P.	OS	51	M	W	34		20/40	$N_2F_0H_0$	5–26–67	PC	6–28–67	1 month	20/30+1	1/1		
	OD [2]	--	--	--			20/25	$N_1F_0H_0$			6–28–67		20/25		$N_2F_0H_1$	

203. C. W.	OS	63	M	W	60	63	20/30	$N_2F_1H_1$	6- 7-66 12-11-67 2- 7-68	PC PC (16)	7-20-68	25 months	HM	19/25	N_2F_2 (R_4).	Vit. hem.
	OD [2]	--	--	--			CF 2′-3′	$N_2F_2H_1$			7-20-68		CF 2′-3′		$N_1F_2H_1$ (R_2).	
204. L. W.	OS	63	F	W	61	63	HM, CF	$N_2F_0H_0$	6- 9-67	PC	9-28-67	4 months	HM	1/4	$N_0F_0H_1$	
	OD [2]	--	--	--			CF 1′	$N_2F_0H_0$			9-28-67		CF 1′			
205. A. B.	OD	30	M	W	2	17	20/20	$N_2F_1H_1$	11-27-67	PC	7- 6-68	8 months	20/25	8/8	$N_0F_1H_0$	
	OS	--	--	--			CF	F_2H_1	6-27-67 8- 3-67	PC PC	7- 6-68	13 months	20/200	13/13	H_2	
206. D. H.	OS	43	M	W	23	39	20/300	$N_1F_1H_1$	6-29-67 11- 9-67 5-30-68	PC PC PC	8-12-68	14 months	20/300	14/14	$N_1F_1H_0$	
	OD [2]	--	--	--			20/300	$N_2F_1H_0$			8-12-68		20/300		$N_2F_2H_1$	
207. H. F.	OD	37	M	W	19	36	CF	H_1	7-17-67	PC	6-15-68	11 months	HM	11/11	H_2	
	OS	--	--	--		36	20/20	$N_2F_0H_0$	7-13-67 11-10-67	PC	6-15-68	do	20/20	11/11	$H_1F_0H_0$	
208. E. L.	OD	54	M	W	50	52	20/80	$N_2F_2H_1$	7-17-67	PC	6-13-68	11 months	HM, CF	11/11	H_2	
	OS [2]	--	--	--			HM				6-13-68		HM			
209. J. S.	OS	44	M	W	38	44	20/200	$N_2F_1H_1$	7-19-67	PC	9- 5-67	2 months	20/100	2/2	$N_2F_0H_1$	
	OD [2]	--	--	--			20/40	$N_2F_0H_0$			9- 5-67		20/100		$N_2F_0H_1$	
210. J. S.	OD	23	M	W	12	23	20/50	$N_2F_1H_1$	7-20-67	PC	7- 6-68	12 months	20/50	12/12	$N_2F_1H_1$	
	OS [2]	--	--	--			20/30	$N_1F_0H_0$			7- 6-68		20/25		$N_2F_0H_0$	
211. E. M.	OD	64	F	W	48	61	CF 18″	$N_2F_0H_1$	7-20-67	PC	8-21-67	1 month	CF 18″	1/1	$N_2F_0H_0$	
	OS [2]	—	—	—			20/400	$N_2F_0H_1$			8-21-67		20/300		$N_2F_0H_1$	
212. O. H.	OS	58	M	W	38	33	20/400	N_1–N_2 F_0–F_1H_1	7-27-67	PC	11-16-57	3 months	HM	3/3	$N_2F_2H_2$	
	OD [2]	—	—	—			CF 16″	$N_2F_2H_1$			11-16-67		20/300		$N_2F_1H_1$	
213. J. H.	OS	25	M	W	11	24	20/300	$N_1F_0H_0$	7-31-67	PC	8-26-67	1 month	20/300	1/1	$N_1F_0H_0$	
	OD [2]	—	—	—			20/50	$N_1F_0H_0$			8-26-67		20/50–1		$N_2F_0H_0$	
214. V. D.	OS	64	F	W	41	58	20/30	$N_2F_1H_0$	8- 3-67 10-4-67 11-27-67 3- 8-68	PC PC PC PC	6- 1-68	10 months	20/50	10/10	$N_1F_1H_0$	
	OD [2]	—	—	—			LP	H_2								

See footnotes at end of table.

E. OKUN AND G. P. JOHNSTON—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last examination	Duration of followup	Visual acuity at last examination	Visual retention index	Classification of retinopathy at last examination	Complications
215. D.H.	OD	62	F	W	42	60	20/400	$N_2F_1H_1$	8- 4-67	PC	8- 6-68	12 months	CF 4′	12/12	$N_2F_2H_1$	
	OS	--	--	--	-------	-------	20/200	$N_2F_1H_0$	3-21-68	PC	8- 6-68	5 months	20/200	5/5	H_2	
									3-25-68	PC						
216. A.T.	OD	43	F	W	28	-------	20/50+	N_2F_1	5-25-64	PC	8-16-67	39 months	20/50	39/39	$N_2F_1H_1$	
	OS	47	--	--	-------	-------	HM 4′	$N_2F_2H_1$ (R_4)	7-14-67	Scl. Bkl.	8-16-67	1 month	LP	0	$N_2F_2H_1$	
217. M.W.	OD	67	F	W	67	67	20/200	$N_1F_0H_1$	6-22-67	PC	6-28-68	12 months	20/200−1	12/12	$N_1F_0H_0$	
									8-15-67	PC						
	OS[2]	--	--	--	-------	-------	20/50	B	----------	----------	6-26-68	----------	20/50	----------	B	
218. B. S.	OD	60	M	W	40	60	20/50	$N_2F_1H_1$	8-17-67	PC	7-10-68	11 months	20/400	11/11	$N_2F_1H_1$	
									1-15-68	PC						
									6-11-68	PC						
	OS[2]	--	--	--	-------	-------	20/40	$N_2F_0H_0$	----------	----------	7-10-68	----------	20/100	----------	$N_2F_1H_0$	
219. H. C.	OD	49	M	W	20	49	20/20	$N_2F_0H_1$	8-18-67	PC	5- 9-68	9 months	20/40	9/9	$N_1F_2H_0$	
	OS[2]	--	--	--	-------	-------	----------	----------	----------	----------	----------	----------	----------	----------	----------	
220. L. W.	OS	61	F	W	49	57	20/100+1	$N_2F_1H_1$	8-23-67	PC	7- 2-68	11 months	20/100+1	11/11	$N_0F_2H_1$	
	OD[2]	--	--	--	-------	-------	LP	----------	----------	----------	7- 2-68	----------	CF	----------	----------	
221. B. G.	OD	23	M	W	8	22	CF 2′-3′	$N_2F_0H_0$	8-13-68	PC	----------	----------	----------	----------	----------	
	OS[2]	--	--	--	-------	-------	20/25+1	$N_2F_0H_0$	----------	----------	----------	----------	----------	----------	----------	
222. D.S.	OS	53	M	W	27	51	20/25	$N_2F_1H_1$	8-29-67	PC	6-24-68	10 months	20/30−2	10/10	$N_2F_1H_1$	
									10-10-67	PC						
									11-14-67	PC						
	OD[2]		--	--	-------	------	Amaur.	----------	----------	----------	----------	----------	----------	----------	----------	
223. H. M.	OS	34	M	W	4	27	20/70	$N_2F_1H_1$	9- 8-67	PC	2- 1-68	5 months	Amaurosis.	----------	$N_2F_2H_1$	Mass of prolif., complete CRA occl.
									9-11-67	PC				5/5		
									10-11-67	PC						
	OD[2]		--	--	-------	-------	20/70−2	$N_2F_1H_1$	----------	----------	2- 1-68	----------	do	----------	----------	

224. E. A.	OD	65	F	W	40	64	20/50—	$N_2F_1H_1$	9-22-67	PC	10- 3-67	11 days		11 days/ 11 days.	$N_2F_1H_1$	
	OS [2]		--	--			HM, CF	H_2			10- 3-67		HM		H_2	
225. A. R.	OS	66	F	W	62	66	20/30	$N_2F_0H_1$	10- 6-67	PC	8- 3-68	10 months	20/200	10/10	$N_1F_0H_0$	
	OD [2]	--	--	--			20/40	$N_2F_0H_0$							$N_2F_0H_0$	
226. P.S.	OD	59	F	W	44	59	20/70	$N_2F_1H_1$	10-13-67	(17)	5- 4-68	6 months	HM	4/6	N_2F_2	
	OS	--	--	--			20/70	$N_2F_1H_1$	10-17-67	PC	5- 4-68	7 months	HM	4/7	N_2F_2	
									12-21-67	Scl. Bkl.						
227. M.N.	OD	63	F	W	57	61	20/400	$N_2F_0H_0$	10-18-67	PC	6-13-68	8 months	CF 4'	8/8	$N_1F_1H_0$	
									5-13-68	PC						
	OS [2]	--	--	--			20/25	$N_2F_0H_0$			6-13-68		20/40—3		$N_1F_0H_0$	
228. R.K.	OD	37	F	W	17	36	CF 3'	$N_2F_0H_1$	10-19-67	PC	8-14-68	10 months	20/30	10/10	$N_1F_0H_0$	
									12-12-67	PC						
									5-28-68	PC						
	OS	--	--	--			20/50	$N_2F_0H_0$			8-14-67		20/30		$N_1F_0H_0$	
229. G.S.	OS [2]	25	M	W	12	25	20/400	$N_2F_0H_1$	10-19-67	PC	7- 3-68	9 months	20/300+1	9/9	$N_2F_1H_2$	Vit. and Mac. hem.
									1- 4-68	PC						
	OD [2]		--				20/100	$N_1F_0H_0$			7- 3-68		20/300		$N_1F_0H_0$	
230. H. D.	OD	44	M	W	34	44	20/30	$N_2F_0H_1$	10-20-67	PC	7-30-68	9 months	20/70+2	9/9	$N_2F_2H_1$	
									11-20-67	PC						
	OS		--	--			20/80	$N_2F_1H_1$	5-24-68	PC	7-30-68	2 months	20/30	2/2	$N_2F_1H_1$	
									5-27-68	PC						
231. M. A.	OD	63	F	W	59	62	20/30	$N_2F_0H_1$	10-26-67	PC	7-22-68	9 months	20/40+	9/9	$N_1F_0H_0$	
	OS		--				20/25+3	N_2F_0	11-28-67	PC	7-22-68	8 months	20/25	8/8	$N_2F_0H_0$	
232. D. M.	OD	29	F	W	15	29	20/25+3	$N_2F_1H_1$	11- 3-67	PC	8- 6-68	9 months	20/70+1	9/9	$N_2F_2H_0$	
									12- 8-67	PC						
	OS [2]						20/20	$N_1F_0H_0$			8- 6-68		20/20		$N_2F_0H_0$	
233. G. E.	OD	57	F	W	42	57	20/400	$N_2F_0H_0$	11-20-67	PC	7- 2-68	8 months	CF 3'	8/8	B	Macular exudates.
	OS [2]		--				CF 2'	$N_2F_2H_1$			7- 2-68		20/100+1		$N_2F_2H_1$ (R_{3+})	
234. F. M.	OD	42	M	W	25	40	20/50	$N_2F_1H_1$	11-21-67	PC	1- 3-68	2 months	20/50+1	2/2	$N_2F_1H_1$	
									12-14-67	PC						
	OS [2]	--	--	--			20/50	$N_2F_2H_1$			1- 3 68		20/300		$N_2F_2H_1$	
235. C. B.	OD	55	M	W	40	55	HM, CF	H_2	12- 5-67	PC	7-31-68	7 months	20/30—3	7/7	$N_2F_1H_0$	
									3-14-68	PC						
	OS	--	--	--			20/50	$N_2F_0H_1$	11-30-67	PC	7-31-68	8 months	20/30	8/8	$N_2F_0H_0$	
									3-14-68	PC						

See footnotes at end of table.

E. OKUN AND G. P. JOHNSTON—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last examination	Duration of followup	Visual acuity at last examination	Visual retention index	Classification of retinopathy at last examination	Complications
236. J. D.	OD	46	M	W	14	25		$N_2F_0H_1$	12- 5-67	PC	5- 1-68	5 months	20/100	5/5	$N_2F_0H_1$	
	OS [2]	--	--	--			20/20	$N_1F_0H_0$			5- 1-68		20/20		$N_2F_0H_0$	
237. M. R.	OS	61	F	W	56	61	CF 6″	$N_2F_2H_1$	12-12-67	PC	4-29-68	4 months	HM	1/4	$N_2F_2H_1$	
	OD [2]	--	--	--			20/30	$N_1F_0H_0$			4-29-68		20/25			
238. F. W.	OS	29	F	W	4	29	20/400	$N_2F_2H_1$	12-19-67	PC	7-22-68	7 months	20/30	7/7	$N_2F_2H_1$ N_1–N_2 F_0H_0	Traction type ret. det. aprx. 3 disc diam. from macula.
	OD [2]	--	--	--			20/25+3	$N_1F_0H_0$			7-22-68		20/25+3			
239. M. S.	OD	42	M	W	35	28	20/50	$N_2F_0H_1$	12-21-67	PC	7- 6-68	7 months	20/40	7/7	B	
	OS [18]	--	--	--					2- 1-68	PC						
240. A. J.	OS	55	M	W	45	47	20/200	$N_2F_1H_1$	1- 4-68	PC	5- 6-68	4 months	20/40–	4/4	$N_2F_1H_1$	Optic atrophy.
	OD [2]	--	--	--			CF 2′	$N_2F_1H_1$			5- 6-68		20/400		$N_2F_1H_1$	
241. E. M.	OS	36	M	W	16	35	20/70	$N_2F_1H_0$	1-10-68	PC	8- 3-68	7 months	20/50	7/7	$N_2F_1H_0$	
	OD [2]	--	--	--			20/300	$N_2F_1H_2$	8- 5-68	PC	8- 3-68		HM		$N_2F_2H_2$	
242. M. L.	OS	43	F	S	21	43	CF 3′	$N_2F_1H_2$	1-11-68	PC	8-12-68	7 months	20/30–2	7/7	$N_2F_1H_1$	
									2- 3-68	PC						
									2-10-68	PC						
	OD [2]	--	--	--			20/50	$N_2F_0H_0$			8-12-68		20/25+		$N_2F_0H_0$	
243. V. B.	OD	44	M	W	20	42	20/300	$N_2F_1H_0$	1-23-68	PC	3- 4-68	2 months	20/400	2/2	$N_2F_1H_0$	
	OS [2]	--	--	--			HM	H_2			3- 4-68		HM			
244. C. H.	OD	28	F	W	15		20/25	$N_2F_1H_1$	1-24-68	PC						
	OS [2]	--	--	--							12- 5-67		HM		$N_2F_2H_1$	
245. I. M.	OS	51	F	W	25	50	20/100+1	$N_2F_1H_1$	1-25-68	PC	7-15-68	6 months	20/200	6/6	$N_2F_1H_1$	Hgb.
	OD [2]	--	--	--					2-27-68	PC						

246. J. S.	OD	63	M	W	49	63	20/40	$N_2F_1H_1$	2-15-68 5- 1-68 7-26-68	PC PC PC	7-25-68	6 months	20/50	6/6	$N_2F_1H_1$	
	OS [2]	--	--	--							2-15-68		NLP			
247. O. R.	OD	51	M	W	21	50	20/25	$N_2F_1H_1$	3- 7-68 4-16-68 5- 2-68	PC PC PC	8- 8-68	5 months	20/25	5/5	$N_2F_1H_1$	Hem. from old PC site 8-8-68.
	OS [2]	--	--	--			CF 18″	H_2			8- 8-68		HM		$N_2F_2H_2$	
248. B. P.	OD	52	F	W	35	52	20/40	$N_2F_0H_1$	3-15-68 5-17-68	PC PC	8- 6-68	5 months	20/40+1	5/5	$N_2F_0H_0$	
	OS	--	--	--			20/50	$N_2F_0H_1$	3-11-68 5-20-68	PC PC	8- 6-68	do	20/30−	5/5	$N_1F_0H_0$	
249. A. P.	OS	55	M	W	51	54	20/200	$N_2F_0H_0$	3-12-68	PC	8-12-68	5 months		5/5	$N_1F_0H_0$	
	OD [2]	--	--	--			20/30	$N_1F_0H_0$			8-12-66		20/70		$N_1F_0H_0$	
250. B. N.	OS	48	F	W	29	47	20/40	$N_2F_1H_1$	3-19-68 5-28-68 8- 1-68	PC PC PC	8-26-68	5 months	CF	5/5	$N_2F_1H_1$	
	OD [2]	--	--	--			20/25+2	$N_2F_0H_0$			8-26-68		20/25		$N_2F_0H_0$	
251. E. A.	OD	34	F	W	14	30	20/70	$N_2F_1H_0$	2- 7-68 8- 9-68	PC PC	8-29-68	6 months	20/40−3	6/6	$N_2F_2H_1$	
	OS	--	--	--			20/70	NFH	2-19-68	([6])	8-29-68	do	20/200	6/6	$N_2F_2H_1$	
252. M. J.	OD	57	F	W	37	55	20/70+1	$N_2F_1H_1$	3-21-68	PC	6- 6-68	3 months	20/70	3/3	$N_0F_1H_1$	
	OS [2]	--	--	--			HM	$N_2F_2H_2$			6- 6-68		HM		H_2	
253. A. F.	OS	55	F	W	33	54	CF 5′	$N_1F_0H_0$	3-26-68	PC	5- 1-68	2 months	CF 3′-4′	2/2	$N_2F_0H_0$	
	OD [2]	--	--	--			20/40	$N_1F_0H_0$			5- 1-68		20/30−2			
254. C. P.	OS	55	F	W	48	55	CF 2′	$N_2F_0H_1$	4- 2-68 7-23-68	PC PC	8-28-68	5 months	20/30	5/5	$N_2F_0H_0$	
	OD [2]	--	--	--			20/20	$N_2F_0H_0$			7-22-68		20/20		$N_2F_0H_0$	
255. E. R.	OS	34	M	W	8	34	CF	$N_1F_0H_1$	4-10-68	PC	6- 1-68	2 months	20/70	2/2	B	
	OD [2]	--	--	--			20/25	$N_1F_0H_0$			6- 1-68		20/20		$N_1F_0H_0$	
256. L. M.	OS	80	F	W	78	79	20/300	$N_2F_0H_0$	4-17-68	PC	7-11-68	3 months	20/200+1	3/3	B	Scattered superficial hem.
	OD [2]	--	--	--			20/70+1	$N_1F_0H_0$			7-11-68		20/70+1		$N_1F_0H_0$	
257. L. G.	OD	63	F	W	33	60	20/70	$N_2F_1H_1$	4-22-68	PC	7- 9-68	2 months	CF 2′	1/2	$N_2F_2H_2$	
	OS [2]	--	--	--			20/300	$N_2F_2H_1$			7- 9-68		CF 1′		$N_2F_2H_2$	
258. C.	OD	59	F	W	39	59	CF 3′-4′	$N_2F_0H_0$	4-29-68	PC	8- 1-68	3 months	CF	3/3	$N_2F_0H_0$	
	OS [2]	--	--	--			20/70+2 20/50PH	$N_2F_0H_0$			8- 1-68		20/50−3		$N_2F_0H_0$	

See footnotes at end of table.

E. OKUN AND G. P. JOHNSTON—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last examination	Duration of followup	Visual acuity at last examination	Visual retention index	Classification of retinopathy at last examination	Complications
259. G. C.	OD	31	M	W	13	31	20/20	$N_2F_1H_0$	5- 6-68	PC	7-13-68	2 months	20/25	2/2	$N_1F_1H_0$	
	OS [2]	--	--	--			20/400	$N_2F_1H_1$			7-13-68		20/400		$N_2F_2H_1$	
260. R. G.	OD	44	F	W	26	43	20/200	$N_2F_0H_1$	5- 8-68	PC	6-20-68	1 month	20/200	1/1	B	
	OS [2]	--	--	--			20/200	$N_2F_1H_0$			6-20-68		20/100		$N_1F_2H_0$	
261. I. F.	OS	53	M	W	29	50	CF 4'-5'	$N_2F_0H_0$	5- 8-68	PC	7-29-68	2 months	CF 3'	2/2	$N_2F_0H_0$	
	OD [2]	--	--	--			20/40+	$N_2F_0H_0$			7-29-68		20/50+		$N_2F_0H_0$	
262. I. M.	OD	51	F	W	25	50	20/30	$N_2F_0H_1$	5-23-68	PC	7-15-68	2 months	20/25+	2/2	$N_2F_0H_0$	
	OS [19]	--	--	--												
263. M. C.	OD	51	F	W	32	44	20/200	$N_2F_0H_0$	5-28-68	PC	7- 2-68	2 months	20/40	2/2	B	
	OS [2]	--	--	--			LP	H_2			7- 2-68		20/200		H_2	
264. E. F.	OS	64	F	W	40	49	CF 3'-4'	$N_2F_1H_0$	5-31-68	PC	8- 3-68	3 months	20/400	3/3	$N_1F_1H_0$	
									7- 8-68	PC						
	OD [2]	--	--	--			20/70	$N_2F_0H_0$			8- 3-68		20/400		$N_2F_0H_0$	
265. R. W.	OD	34	M	W	17	34	20/30	$N_2F_0H_0$	6- 3-68	PC	7- 9-68	1 month	20/25	1/1	$N_1F_0H_0$	
	OS [2]	--	--	--			HM	H_2			7- 9-68		HM		H_2	
266. M. C.	OD	59	F	W	53	59	20/30	$N_2F_0H_1$	6-10-68	PC	7- 9-68	1 month	20/50	1/1	B	
	OS [2]	--	--	--			20/25	$N_1F_0H_0$			7- 9-68		20/25		$N_1F_0H_0$	
267. P. Y.	OD	25	F	W	7	22	20/20	$N_2F_1H_1$	6-11-68	PC	8-19-68	2 months	20/20	2/2	N_2F_0-	
									7-16-68	PC					F_1H_1	
									8-20-68	PC						
	OS [2]	--	--	--			HM, CF	$N_2F_2H_1$			8-19-68		20/300		H_1-H_2	

268. R. R	OD	43	F	W	23	43	20/400	$N_2F_0H_1$	6-11-68 6-27-68 8-13-68	PC PC PC	8-12-68	2 months	20/30	2/2	$N_2F_1H_1$	
	OS [2]	--	--	--			20/40	$N_2F_0H_0$			8-12-68		20/30		$N_2F_0H_0$	
269. R. S	OD	52	M	W	27	50	20/200	$N_2F_0H_1$	6-13-68	PC	7- 8-68	1 month	20/70	1/1	$N_2F_0H_0$	
	OS [2]	--	--	--												
270. G. C	OD	54	M	W	17	51	20/50	$N_2F_1H_2$	6-17-68	PC	7-30-68	1 month	20/70	1/1	$N_2F_1H_1$	
	OS [2]	--	--	--			HM				7-30-68		HM			
271. C. B	OD	61	M	W	34	61	20/400	$N_2F_0H_1$	7- 2-68	PC	8-12-68	1 month	20/40+3	1/1	$N_1F_0H_0$	
	OS [2]	--	--	--			20/25	$N_2F_0H_0$			8-12-68		20/20-2		$N_2F_0H_0$	
272. E. G	OS	25	M	W	5	21	20/30	$N_2F_0H_1$	7- 2-68 7-18-68	PC PC	8-12-68	1 month	20/30	1/1	$N_2F_0H_1$	
	OD [2]	--	--	--			HM	H_2								
273. W. R	OS	67	M	W	55	65	20/70	$N_2F_2H_1$	7- 3-68	PC	8- 3-68	1 month	20/70- 20/50 PH.	1/1	$N_1F_2H_1$	
	OD [2]	--	--	--			CF 2′	$N_2F_2H_1$			8- 3-68		CF 2′			
274. W. M	OD	58	M	W	54	57	20/70+2	$N_1F_0H_0$	7- 8-68	PC	8- 1-68	1 month	20/400	1/1	$N_2F_0H_0$	
	OS [2]	--	--	--			20/50	$N_1F_0H_0$			8- 1-68		20/50+2		$N_1F_0H_0$	
275. R. M	OS	34	M	W	11	34	20/70+2	$N_2F_2H_1$	7- 9-68	PC	7-22-68	13 days	20/30+2	13 days/ 13 days	$N_2F_2H_2$ (R_1)	
	OD [2]	--	--	--			20/25+2	$N_2F_0H_0$			7-22-68		20/25		$N_2F_0H_0$	
276. G. E	OD	33	M	W	16	33	20/25-3	$N_2F_0H_1$	7- 9-68 7-30-68	PC PC	8-14-68	1 month	20/30	1/1	$N_2F_0H_1$	
	OS [2]	--	--	--			CF	H_2			8-14-68		HM		H_2	
277. D. W	OS	28	M	W	10	28	20/20	$N_2F_1H_0$	7-16-68	PC	8-19-68	1 month	20/20	1/1	$N_2F_1H_0$	
	OD [2]	--	--	--			20/20	$N_2F_1H_0$			8-19-68		20/20		$N_2F_1H_0$	
278. B. M	OS	70	F	W	60	70	20/40	$N_1F_0H_0$	7-16-68	PC	8-14-68	1 month	20/40	1/1	$N_1F_0H_0$	
	OD [2]	--	--	--			20/30	$N_1F_0H_0$			8-14-68		20/30		$N_1F_0H_0$	
279. P. S	OD	43	M	W	25	43	20/25-3	$N_2F_1H_1$	7-22-68	PC	8- 3-68	12 days	20/200+1	12 days/ 12 days	$N_1F_1H_1$	Reaction centrally w/edema into macula.
	OS [2]	--	--	--			20/300	$N_2F_2H_1$			8- 3-68		20/300		$N_2F_2H_1$	

See footnotes at end of table.

333-611 O - 69 - 54

E. OKUN AND G. P. JOHNSTON—Continued

Number and patient	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last examination	Duration of followup	Visual acuity at last examination	Visual retention index	Classification of retinopathy at last examination	Complications
280. V. W.	OD	35	F	W	7	34	20/70		7-29-68	Scl. Bkl.					$N_2F_2H_1$	
	OS	--	--	--			20/30	$N_2F_0H_1$[21]	10-18-67	PC	7-27-68	10 months	20/25	10/10	B	
									6- 7-68	PC						
281. R. B.	OS	17	M	W	3	17	20/30	$N_2F_1H_1$	7-30-68	PC	8-14-68	1 month	20/40-2	1/1	$N_2F_1H_1$	
	OD [2]	--	--	--			CF	H_2			8-14-68		20/300			
282. V. V.	OD	29	F	W	7	29	20/50	$N_2F_2H_1$	8- 9-68	([6])						
	OS	--	--	--			20/70	$N_2F_2H_1$	7- 2-68	PC						
									7-11-68	PC						
283. G. B.	OD	55	F	W	54	55	20/50	$N_2F_0H_0$	11- 8-65	PC	7-26-67	20 months	20/60	20/20	$N_1F_0H_0$	
	OS [2]	--	--	--			20/25	$N_2F_0H_0$			7-26-67	do	20/40	20/20	$N_2F_0H_0$	

[1] Scleral Buckle with encircling polyethylene tube and foam rubber implant.
[2] Not treated.
[3] Not treated (anopthalmos).
[4] Cryotherap to proliferated stalk on disc.
[5] Duration of diabetes 23 years.
[6] Cryohypophysectomy.
[7] NLP (bullous kerotopathy, rubeosis iridis).
[8] Can read large print.
[9] N_2F_2 with detachment.
[10] Cryo and cyclocryotherapy.
[11] Latent diabetes.
[12] PC and Scleral Buckle.
[13] PC and Revised Scleral Buckle.
[14] Diabetic for 22 years.
[15] Stalk sectio and partial hypophysectomy.
[16] Scleral Buckle with plombage.
[17] Scleral Buckle and resection.
[18] Not treated (enucleated, traumatic laceration, age 19).
[19] See No. 249.
[20] Not treated (enucleated).
[21] F_1 off disc.

Appendix L

N. H. ROTH AND R. W. RAND

(DATA FROM CHAPTER 43)

[Mode of therapy—LIGHT COAGULATION]

Patient No.	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Date of last exam	Duration of followup (months)	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Complications	Results [1]
1.	R L	38 --	M --	C --	16	33	20/60 CF	$N_2F_1H_1$ H_2	11-66	8-68	21	HM 1′ HM 1′	4/21	$N_2F_2H_1$ $N_2F_2H_1$	Continued hemorrhages, poor control of diabetes.	P
2.	R L	43 --	M --	C --		40	20/30+1 20/30+3	$N_2F_0H_1$ $N_2F_0H_0$	8-9-68 8-22-68	8-30-68 8-30-68	(2) (2)	20/30 20/30	½/½ ¼/¼	$N_1F_0H_1$ $N_1F_0H_0$	None do	S S
3.	R	57	F	C	27	52	20/40	$N_1F_2H_0$	5-27-68	8- 5-68	3	20/40-1	3/3	$N_1F_2H_0$	None	S
4.	R	29	F	C	6	28	20/25+2	$N_2F_2H_1$	6- 5-68	8-13-68	2	20/30+2	2/2	$N_1F_2H_1$	None	S
5.	R L L	22 -- --	M -- --	C -- --	2	20	20/200 20/60+3	$N_2F_2H_1$ $N_1F_2H_0$	4-27-66 7- 6-66 5-20-68	7-29-68 7-29-68 7-29-68	27 25	20/200+2 20/50-1	27/27 25/25	$N_1F_2H_1$ $N_1F_2H_0$	None do	S I
6.	L	32	F	C	5	27	20/60	$N_2F_2H_1$	4-12-68	7- 8-68	3	20/60+2	3/3	$N_1F_2H_0$	None	S
7.	R	30	M	C	15	28	CF 4′	$N_2F_2H_1$	1- 5-68	4-18-68	6	HM 2′	0/6	$N_2F_2H_1$	Progression of disease, deceased 6-68.	P
8.	R L	71 --	M --	C --	67	71	20/200+1 CF 1′	$N_2F_2H_0$ F_2H_2	4-17-68	6-25-68	2	20/200+1	2/2	$N_2F_2H_0$ F_2H_0	None	S
9.	L R	66 --	F --	C -	62	66	20/50-2	$N_2F_0H_1$ B	6-10-68	8-20-68	2	20/200	2/2	B B	None	S

N. H. ROTH AND R. W. RAND—Continued

Patient No.	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Date of last exam	Duration of followup (months)	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Complications	Results [1]
10.	R	25	M	C	7	25	20/25−2	$N_2F_0H_0$	7-24-68	8-20-68	1	20/25−2	1/1	$N_2F_0H_0$	None	S
	L	--	--	--			20/100	$N_2F_2H_1$				20/200		$N_2F_2H_1$		
11.	R	47	M	C	19	44	20/50−1	$N_2F_1H_0$	9-23-66	7- 2-68	22	20/70−1	22/22	$N_1F_1H_0$	None	S
	R	--	--	--				$N_2F_1H_0$	11-25-66							
	R	--	--	--				$N_2F_1H_0$	1-26-68							
	L	--	--	--			20/30+2	$N_1F_1H_0$				20/25+3		$N_1F_1H_0$		
12.	L	33	M	C	10	32	CF 1-2′	$N_2F_2H_1$	2-23-68	4-29-68	2	CF 1-2′	1/1	$N_2F_2H_1$	New retinal hemorrhages.	S
	R	--	--	--			20/40+1	$N_2F_2H_0$	3-29-68		1	20/40+1	2/2	$N_2F_2H_0$	Cryohypophysectomy 6-11-68.	S
13.	R	55	M	C	30	52	HM 3′	$N_2F_2H_1$				HM 3′		$N_2F_2H_1$		
	L	--	--	--			20/20−1	$N_2F_2H_1$	3-22-67	4- 4-67	1	20/20−	1/1	$N_2F_2H_1$	None	S
14.	R	39	M	C	3	37	20/70	$N_2F_2H_1$	3-6-68	8-1-68	5	20/30−1	5/5	$N_1F_2H_0$	None	S
	L	--	--	--			20/60+1	$N_2F_2H_0$	3-27-68		5	20/60−1	5/5	$N_1F_2H_0$	do	S
	R	--	--	--					6-14-68							
15.	L	56	F	C	43	54	20/70−1	$N_2F_2H_1$	5-15-67	8-68	15	20/100−1	7/15	$N_2F_0H_1$	No hemorrhages at present.	P
	R	--	--	--			20/80+3	$N_2F_2H_1$	8-21-67	8-68	12	20/100−1	2/12	$N_1F_0H_0$		
	L	--	--	--					10-22-67							S
16.	L	47	M	C	18	45	20/80+2	$N_2F_0H_0$	7-3-67	7-29-68	14	20/200	3/14	$N_1F_0H_0$	Vitreous hemorrhage after LC, coronary 7-67.	P
	R	--	--	--			20/60	$N_1F_0H_0$	7-28-67	7-29-68	13	20/70−1	14/14	$N_1F_0H_0$		S
17.	R	43	F	C	24	36	20/40−1	$N_2F_1H_1$	1-18-67	4-2-68	15	20/30−2	15/15	$N_2F_1H_0$	Macular traction, put on PAS 7-67.	I
	L	--	--	--			20/40	$N_2F_1H_1$	1-18-67	4-2-68	15	20/80−1	13/15	$N_2F_1H_0$		
	R	--	--	--			20/40+1		6-2-67	4-2-68						P
18.	R	68	M	C			20/200		3-29-67	6-15-67	3	20/200	3/3		None	P
	L	--	--	--			20/40+3		3-29-67	6-15-67	3	20/70−1	2/3		do	S
19.	R	52	M	C	35	51	20/60+4	$N_2F_0H_1$	11-10-67	6-11-68	7	20/30+3	7/7	$N_2F_0H_0$	Start on PAS 1-68	I

20.	R	58	M	C	36	54	20/80+1	N_2	12-21 66	4- 4-68	20	20/200-1	11/20	$N_1F_0H_0$	Macular hemorrhage and exudates.	P
	L	--	--	--			20/50	N_2	1-20-67	4- 4-68	19	20/25	19/19	$N_1F_0H_0$		I
21.	L	58	M	C	40	50	20/25+1	$N_2F_1H_0$	8- 6-65	8-21-68	37	20/200	28/37	$N_2F_0H_0$	Hemorrhage over macula.	P
	R	--	--	--			20/20	$N_2F_1H_0$	10- 1-65	8-21-68	35	20/25	35/35	$N_2F_0H_0$		I
22.	L	48	F	C		44	20/50	$N_2F_2H_1$	4-27-67	8-13-68	16	20/200+2	9/16	$N_2F_2H_1$	Increasing vitreous hemorrhages, put on PAS 1-68.	P
23.	R	56	M	C		55	CF 3′	$N_2F_1H_0$	7-15-68	8- 8-68	1	CF 3′	1/1	$N_2F_1H_0$	Macular destruction	S
24.	R	24	M	C		25	20/200	$N_2F_1H_1$	7-14-67	11-27-67	4	CF	0/4		Developed secondary glaucoma.	P
	L	--	--	--			20/200+1	$N_2F_1H_1$	7-14-67	11-27-67	4	CF	0/4	$N_2F_1H_1$	None	P
	L	--	--	--					11- 3-67					$N_2F_1H_1$		
25.	L	48	M	C	44	45	20/100-1	$N_2F_1H_0$	7-10-67	3-21-68	8	HM 6′	1/8	$N_2F_1H_0$	Deceased 6-2-68	P
	R	--	--	--			20/25	$N_1F_1H_0$	8-21-67	3- 2-68	7	20/25-2	7/7	$N_1F_1H_0$		S
26.	L	38	M	C	10	35	20/25-3	$N_2F_1H_1$	11-17-67	8-20-68	9	20/25-1	9/9	$N_2F_1H_0$	None	S
	R	--	--	--			20/20	$N_2F_1H_0$	6-26-68	8-20-68		20/25-2	2/2	$N_2F_1H_1$	do	S
27.	L	53	F	C	33	51	20/30-1	$N_2F_2H_1$	7-15-68	8-21-68	1½	20/40	1½/1½	$N_2F_2H_1$	None	S
28.	R	53	M	C			20/70-2	$N_2F_0H_1$	5-31-67	7- 2-68	14	20/60	14/14	$N_1F_0H_0$	None	I
	L	--	--	--			20/40	$N_2F_0H_0$	4- 1-68	7- 2-68	3	20/40	3/3	$N_2F_0H_0$	None	S
29.	R	82	F	C	78	79	20/60									
	L	--	--	--			CF 10′	$N_1F_0H_0$	1-27-67	6-27-68	17	CF 1′	17/17	$N_1F_0H_0$	Macular involvement.	S
30.	R	60	M	C	60	59	20/400	$N_2F_2H_1$	6- 5-68	8-26-68	3	CF 5′	2/3	$N_2F_2H_0$	None	P
	L	--	--	--			20/100+2	$N_2F_1H_1$	7-12-68	8-26-68	2	20/200	1/2	$N_2F_1H_1$		P
31.	R	35	M	C	8		LP	$N_2F_2H_1$				LP				S
	L	--	--	--			20/30	$N_2F_1H_0$	3-13-67	6-28-67	3	20/30	3/3	$N_1F_1H_0$	New retinal hemorrhages, cryohypophysectomy 6-28-67.	
32.	R	60	F	C	47	58	20/40-2					20/30-1				
	L	--	--	--			20/50-2	$N_2F_0H_0$	1-67	6-68	17	20/30-2	17/17	$N_1F_0H_0$	None	I
	L	--	--	--					12-67							

[1] I=Improved; S=stable; P=progressed.
[2] 1 to 2 weeks.

Appendix M

H. F. SPALTER, G. M. HOWARD, AND C. CAMPBELL

(DATA FROM CHAPTER 44)

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last exam	Duration of follow-up	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Complications
1. J. B.	R	70	F	W	55	65	CF 3′						CF 3′			
	L	--	--	--			6/300	$N_1F_0H_1$	6- 4-68	Xenon arc	8-22-68	11 weeks	6/300	1	$N_1F_0H_0$	
2. P. B.	R	41	M	W	9	34	20/30	$N_1F_0H_1$	2- 8-68 2-27-68	Xenon arc	4-29-68	6 months	20/30	1	$N_0F_0H_0$	
	L	--	--	--			20/30						20/25			
3. L. B.	R	69	F	W	51	69	20/40	$N_1F_1H_1$	5- 2-68 5-29-68	Xenon arc	6-11-68	1 month	20/40	1	BH_0	
	L	--	--	--			20/40						20/40			
4. J. C.	R	64	M	W	34	54	10/300	$N_1F_0H_1$	11- 9-67	Xenon arc	8-23-68	9 months	10/300	1	BH_0	
	L	--	--	--			13/300	$N_1F_0H_1$	12-21-67 4-24-68	do	8-23-68	8 months 4 months	13/300	1	BH_0	
5. J. C.	R	63	M	W	53		>20/300						>20/300	1	BH_0	
	L	--	--	--		61	20/300	$N_2F_0H_0$	2-28-68 5- 2-68	Xenon arc	8-20-68	7 months	20/300	1	$N_2F_0H_0$	
6. E. D.	R	62	M	W	59		LP	H_2					LP			
	L	--	--	--		59	18/300	$N_2F_0H_1$	6- 3-68	Xenon arc	8-17-68	10 months	CF	.6	$N_2F_0H_1$	Hemorrhage.
7. F. E.	R	47	F	W	20	44	20/40	$N_0F_2H_1$	12- 2-66 2- 9-67	Xenon arc Laser.	6-12-68	21 months	CF	.05	$N_0F_2H_1$	Retinal detachment.
	L	--	--	--			LP	H_2					CF		$N_0F_2H_1$	
8. M. F.	R	76	M	W	54	54	20/50									
	L	--	--	--			20/100	$N_1F_0H_0$	1-24-68	Xenon arc	6-18-68	5 months	20/50	1	B	

9. E. F.	R	64	F	W	59		20/30						20/30			
	L	--	--	--		64	20/200	$N_1F_0H_0$	5- 9-68	Xenon arc	6-18-68	6 weeks	20/200	1	B	
10. C. F.	R	76	M	W	74	76	HM 1′	$N_0F_2H_1$	6-11-68	Laser	8-30-68	11 weeks	CF 2′	1	$N_0F_2H_1$	
	L	--	--	--			CF 2′	$N_0F_2H_1$					CF 3′		$N_0F_2H_1$	
11. P. G.	R	53	M	W	8	52	5/300	$N_1F_1H_0$	2- 7-68	Xenon arc	6-13-68	4 months	5/300	1	$N_1F_1H_0$	
	L	--	--	--			8/300	$N_1F_1H_0$	1-11-68	do	6-13-68	5 months	8/300	1	$N_1F_1H_0$	
12. G. D.	R	55	M	W	53	53	CF 4′	$N_2F_2H_1$	7- 1-68	Xenon arc	9- 9-68	2 months	CF 4′	1	$N_2F_2H_1$	
	L	--	--	--			LP	H_2					LP	1	H_2	
13. E. H.	R	54	F	W	26	51	5/300	$N_1F_0H_1$	5-18-67 6-22-67 11-17-67	Xenon arc	9- 4-68	16 months	20/300	1	B	
	L	--	--	--			20/40	$N_1F_0H_1$	5- 2-68 6-21-68	do	9- 4-68	4 months	20/50	1	B	
14. J. J.	R	34	M	W	21		20/40	$N_2F_0H_1$					20/20			
	L	--	--	--		33	20/80	$N_1F_0H_1$	6-12-68	Xenon arc	8-30-68	2 months	20/400	.15	$N_1F_0H_1$	Vitreous hemorrhage.
15. R. K.	R	76	F	W	51	74	10/300	BH_0	8-20-68	Xenon arc	9- 4-68	1 month	10/300	1	BH_0	
	L	--	--	--			10/300	BH_0					10/300	1		
16. M. K.	R	61	M	W	50	58	20/300									
	L	--	--	--			5/300	B	1- 8-68	Xenon arc	Patient expired					
17. B. L.	R	62	M	W	45	60	20/40	$N_1F_1H_1$	1-10-68	Xenon arc	9-12-68	8 months	10/100	.2	$N_1F_0H_0$	
	L	--	--	--			20/60	$N_1F_1H_1$	8-31-67 10-25-67 6- 6-68	do	9-12-68	1 year	HM	.8	$N_1F_2H_0$	
18. D. L.	R	43	M	W	23	42	20/25	BH_1	7- 2-68	Xenon arc	7-11-68	9 days	20/25	1	B	
	L	--	--	--			10/300	$N_1F_0H_0$	11- 6-67	do	7-11-68	10 months	20/300	1	$N_1F_0H_0$	
19. J. L.	R	68	M	W	43	66	20/300	$N_2F_2H_1$	7- 8-68	Laser	9- 3-68	2 months	20/400	1	$N_2F_2H_1$	
	L	--	--	--			20/60	$N_2F_2H_0$					20/60	1	$N_2F_2H_0$	
20. J. M.	R	37	M	W	14	37	20/20	$N_1F_1H_1$	2-28-68 9-11-68	Xenon arc	9-19-68	7 months	20/20	1	B	
	L	--	--	--			LP	H_2					LP	1	H_2	
21. E. M.	R	52	M	N	50	52	20/50	$N_1F_0H_0$	5-31-68	Xenon arc	8-28-68	6 weeks	20/60	1	B	
	L	--	--	--			CF	$N_2F_2H_0$					CF	1	$N_2F_2H_0$	

See footnotes at end of table.

H. F. SPALTER, G. M. HOWARD, AND C. CAMPBELL—Continued

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last exam	Duration of follow-up	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Complications
22. N. M.	R	36	F	W	1½	34	20/30	$N_2F_2H_0$	4-30-68	Xenon arc	8-29-68	4 months	20/25	1	B	
	L	--	--	--			20/70	$N_2F_2H_0$	5-23-68	do	8-29-68	3 months	3/300	.3	$N_2F_2H_0$	Retinal detachment.
23. H. O.	R	57	M	W	47	57	20/25	B					20/25	1	B	
	L	--	--	--			20/40	$N_1F_1H_0$	5- 2-68	Xenon arc	9- 1-68	4 months	20/40	1	B	
24. E. R.	R	24	F	W	9		20/25						20/25	1	$N_1F_0H_0$	
	L	--	--	--		23	20/300	$N_1F_1H_1$	12-21-67	Xenon arc	6-12-68	6 months	20/40	1	$N_1F_0H_0$	
25. E. R.	R	53	F	W	33	53	20/40	BH_0	4-17-68	Xenon arc	9-10-68	5 months	20/50	1	BH_1	
	L	--	--	--			20/40	BH_0	6-24-68	do	9-10-68	3 months	20/30	1	B	
26. C. R.	R	51	M	W	46	51	CF	B	4-29-68	Xenon arc	8-27-68	4 months	8/300	1	B	
	L	--	--	--			20/50	B	5-30-68	do	8-27-68	3 months	20/50	1	B	
27. A. R.	R	52	M	W	46	52	20/50	$N_1F_1H_1$	7- 2-68 8-29-68	Xenon arc	9-18-68	2 months	20/50	1	BH_0	
	L	--	--	--			3/300	BH_1					3/300	1	BH_1	
28. W. R.	R	45	M	W	36	44	20/40	$N_1F_0H_0$	6-24-68	Xenon arc	8-20-68	2 months	20/40	1	B	
	L	--	--	--			20/40	$N_1F_0H_0$	5-20-68	do	8-20-68	3 months	20/40	1	B	
29. R. R.	R	66	F	W	46		20/40	$N_2F_0H_0$					20/40	1		
	L	--	--	--		65	20/200	$N_2F_0H_0$	6-21-68 6-28-68	Xenon arc	8-30-68	2 months	20/40	1	$N_1F_0H_0$	
30. A. S.	R	24	F	W	10	12	LP	$N_0F_2H_1$					LP	1	$N_0F_2H_1$	
	L	--	--	--			CF 2′	$N_0F_2H_1$	11-30-67 3- 1-68	Xenon arc	8-28-68	9 months	CF 3′	1	$N_0F_2H_1$	
31. H. S.	R	56	F	W	46	50	5/300	$N_0F_2H_0$					CF		$N_0F_2H_0$	
	L	--	--	--			HM	$N_0F_2H_0$	2- 1-68 2- 1-68	Laser Xenon arc	6- 7-68	4 months	HM	1	$N_0F_2H_0$	Vitreous hemorrhage.

32. M. S	R	55	M	W	35	54	7/300	$N_0F_2H_1$					7/300	1	$N_0F_2H_1$	
	L	--	--	--			20/200	$N_1F_1H_1$	5-27-68	Xenon arc	6- 4-68	1 month	20/200	1	$N_1F_1H_0$	
33. P. S	R	58	M	W	33	58	20/100	$N_1F_0H_1$	9-20-68 8-20-68	Xenon arc	9-20-68	1 month	20/30	1	B	
	L	--	--	--			HM	H_2					HM		H_2	
34. C. T	R	19	F	W	1	15	20/30	$N_2F_0H_0$	5-10-68 6-25-68 9-24-68	Laser do Xenon arc	9-24-68	4 months	20/30	1	$N_2F_0H_0$	
	L	--	--	--			20/30	$N_2F_0H_0$					20/25	1	$N_2F_0H_0$	
35. P. U	R	68	F	W	62	68	20/300	B	7- 5-68	Xenon arc	9- 4-68	2 months	20/300	1	B	
	L	--	--	--			20/300	B					20/300		B	
36. J. V	R	43	M	W	23	40	LP	H_2								
	L	--	--	--			20/400	$N_1F_0H_1$	8-20-68	Xenon arc	8-21-68		20/50	1	BH_1	
37. G. V	R	62	M	W	12	56	20/300	B					20/300		B	
	L	--	--	--			20/300	B	12-21-67 6- 5-68	Xenon arc	8-21-68	8 months	20/300	1	B	
38. M. W	R	55	F	W	43	52	1/300	$N_0F_2H_0$	7- 6-67	Xenon arc	8-20-68	13 months	5/300	1	$N_0F_2H_0$	
	L	--	--	--			3/300	$N_0F_2H_0$	10-22-67	do	8-20-68	9 months	3/300	1	$N_0F_2H_0$	
39. F. W	R	54	M	W	36	53	20/300	$N_1F_1H_0$	2-11-68	Xenon arc	8-27-68	6 months	20/300	1	$N_0F_1H_0$	
	L	--	--	--			20/300	$N_1F_0H_1$	4-10-68 6-18-68	do	8-27-68	4 months	20/80	1	$N_1F_1H_0$	
40. J. D	R	57	F	N	39	55	20/25	$N_2F_1H_1$	10- 6-67 12-27-68	Xenon arc	6-24-68	11 months	20/50	1	$N_0F_2H_0$	
	L	--	--	--			20/200	$N_2F_2H_1$	10- 6-67 12-27-68	do	6-24-68	11 months	10/300	.87	$N_1F_2H_1$	
41. F. T	R	44	M	W	13	30	20/20	$N_1F_0H_0$	9-24-68	Xenon arc	9-24-68		20/20	1	$N_1F_0H_0$	
	L	--	--	--			20/20	$N_1F_0H_1$	5-29-68 9-24-68	do	9-24-68	4 months	20/20	1	$N_1F_0H_0$	
42. A. P	R	28	F	W	9	27	20/200	$N_1F_0H_1$	9- 3-68	Xenon arc	9-16-68	13 days	20/200		B	Previous laser treatment 1 year ago elsewhere.
	L	--	--	--			20/200	B					20/200		B	
43. J. N	R	62	F	W		61	20/70	B					20/70		BH_1	
	L	--	--	--			20/200	$N_1F_0H_1$	6-27-68	Xenon arc	8-16-68		CF	.3	BH_1	Vitreous hemorrhage.

See footnotes at end of table.

H. F. SPALTER, G. M. HOWARD, AND C. CAMPBELL—Continued

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last exam	Duration of follow-up	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Complications
44. F. T.	R	55	F	W	35	50	LP	$N_2F_2H_0$					LP		$N_2F_2H_0$	
	L	--	--	--			LP	$N_2F_2H_0$	9- 5-68	Laser	9-26-68	21 days	LP	1	$N_2F_2H_0$	
45. R. S.	R	46	M	W	26	26	20/50	B	9- 6-68	Xenon arc	9-12-68	6 days	20/50	1	B	
	L	--	--	--			20/20	$N_1F_0H_0$							B	
46. O. T.	R	65	M	W	45	62	20/50	$N_1F_1H_1$					20/50	1	$N_1F_1H_1$	
	L	--	--	--			20/200	$N_1F_1H_1$	9-18-68	Xenon arc	9-18-68		20/200	1	$N_1F_1H_1$	
47. J. G.	R	62	M	W	37	61	LP	H_2								
	L	--	--	--			20/80	$N_1F_0H_1$	9-10-68	Xenon arc	9-10-68		20/80		$N_1F_0H_1$	
48. E. S.	R	68	M	W	63	62	20/100	BH_0	9-16-68	Xenon arc	9-16-68		20/100		BH_0	
	L	--	--	--			20/40	BH_0							BH_0	
49. M.	R	45	F	W	27	41	HM	H_2	None						H_2	
	L	--	--	--			20/80	$N_1F_2H_0$	6-25-68	Laser	9-10-68	3 months	20/80	1	$N_1F_2H_1$	Vitreous hemorrhage mild.
50. Sa.	R	57	F	W	35	53	20/50	$N_1F_1H_1$	8-23-67 8-20-68 1-17-68	Xenon arc and laser.	8-20-68	1 year	20/70	.5	$N_1F_2H_1$	Increasing retinal disease.
	L	--	--	--			LP	H_2	None						H_2	
51. Se.[2]	R	27	F	W	8	25	20/200	H_2	2- 1-67	Pituitary ablation.	3-29-68	13 months	NLP	.1	$N_2F_2H_1$	
	L	--	--	--			20/400	$N_1F_1H_1$	5-15-67	Laser	3-29-68		LP	.1	$N_2F_2H_1$	
52. C.	R	48	F	W	41	47	1/200	H_2	1-29-68	Xenon arc	6-24-68	13 months	20/40	1	$N_1F_1H_1$[3]	
	L	--	--	--			6/200	$N_1F_2H_1$	1-29-68 5-16-67	do	6-24-68		2/200	.5	$N_1F_2H_1$	
53. Le.	R	38	F	W	16	37	20/30	$N_2F_0H_0$	11-10-67	Xenon arc	8-21-68	9 months	20/30	1	$N_1F_0H_0$	
	L	--	--	--			20/200	$N_1F_2H_1$	None				1/200		$N_1F_2H_1$	

54. Q	R	53	F	W	31	52	20/40	$N_1F_1H_0$	1-18-67 1-16-68	Laser do	6-27-68	18 months	20/50	.8	$N_1F_1H_0$	
	L	--	--	--			LP	H_2					LP		H_2	
55. H	R	71	M	W	55	50	20/70	$N_1F_1H_1$	3- 5-68	Xenon arc and laser.	9-12-68	6 months	20/70	1	$N_1F_1H_1$	
	L	--	--	--			2/200	H_2					HM		H_2	
56. La	R	47	F	W	27	46	20/25	$N_1F_1H_0$	3-13-68 8-16-68 9-25-68	Laser x3	9-11-68	6 months	20/40	.5	$N_1F_2H_1$	
	L	--	--	--			3/200	$N_1F_2H_0$	8-16-68	Laser	9-11-68	1 month	3/200	1	$N_1F_2H_0$	
57. K. K	R	71	M	W	56	71	20/20-3	N_1F_0	12-12-67 1-30-68	Xenon	9- 9-68	10 months	20/30-	.8	B	
	L	--	--	--		68	20/60-2	N_2F_1		None			20/100-1		F_2	
58. S.K	R	33	M	--	14	30	20/400-	H_1F_2		None			20/400-		F_2H_1	
	L	--	--	--		33	20/20-1	$N_1F_1H_1$	7-23-68	Xenon	8- 5-68	3 weeks	20/20-1	1	F_1H_1	
59. S. R	R	23	F	W	11	None	20/20-1	N_1F_1	7-23-68	Xenon	8-21-68	4 weeks	20/25-	.2	F_1	
	L	--	--	--		23	20/400-	F_2		None			20/400-		F_2	
60. E. K	R	35	M	--	9	None	20/20-1	F_1	8- 2-68	Xenon	9-13-68	4 weeks	20/20	1	F_1	
	L	--	--	--		35	20/400-	H_2		None			20/400-		H_2	
61. D. N	R	40	M	W	5	32	20/70-	N_2F_2		None			20/70-		N_2F_2	
	L	--	--	--		32	20/70-	N_1F_1	9-17-68	Xenon	9-20-68	3 days	20/400	.3	F_1	
62. F. H	R	35	M	W	15	None	20/20-3	N_1F_1	7- 5-67 10-24-67 8- 5-68	Xenon	8- 6-68	14 months	20/20-	1	F_1	
	L	--	--	--		33	20/400-	F_2		None			20/400-		F_2	
63. G. M	R	45	F	--			20/400-	F_2		None			20/400-		F_2	
	L	--	--	--			20/400	B	7-15-68 8- 1-68 8-15-68 9- 3-68	2 laser 2 cryo	9-25-68	1 month	20/400	1	B	
64. V. F	R	38	F	W			20/30	F_1		None			20/20-1		F_1	
	L	--	--	--			20/30	F_1	2- 9-67 3-30-67 6- 5-67	Laser	6-15-68	16 months	20/50-3	.8	B	
65. C. J	R	56	F	N	52	55	20/400-	F_2	3- 1-67 3-15-67 6-15-67	Laser	6-27-58	15 months	20/400-	1	F_2	
	L	--	--	--		55	20/100-2	F_1		None			20/400-		F_2	

See footnotes at end of table.

H. F. SPALTER, G. M. HOWARD, AND C. CAMPBELL—Continued

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date of therapy	Mode of therapy	Date of last exam	Duration of follow-up	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Complications
66. S. F.	R	20	F	W	5	15	20/400—	F_2	6-15-65	T. C. pit. abl.	5- 8-67	2 years	20/400—	1	F_2	
	L	--	--	--		17	20/80—	F_1	11- 7-67	Xenon			20/400—	.5	B	
67. J. S.	R	25	M	W	10	None	20/20	B	1-14-67	T. C. pituitary ablation.	8- 8-68	19 months	20/400—	.05	H_2	
	L	--	--	--		24	20/400—	H_2					20/400—	1	H_2	
68. D. V.	R	35	M	W	5	33	20/20—2	N_2F_1		None	8- 9-68		20/20		N_2F_1	
	L	--	--	--		33	20/20—1	N_2F_1	3- 1-68 7-16-68	Xenon	8- 9-68	5 months	20/20		F_1	
69. R. G.	R	36	M		18	35	20/20	N_1F_1	4-30-68	Xenon	6- 4-68	5 weeks	20/30—	.5	F_2	
	L	--	--	--		34	20/400	F_2		None	6- 4-68		20/400		F_2	
70. T. D.	R	48	M	W	19	47	20/400	F_1H_1	6-28-68	Xenon	9-11-68	2½ months	20/200	1	F_2	
	L	--	--	--		47	20/30—2	F_2H_1	6- 4-68	do	9-11-68	3 months	20/400—	.3	H_2	
71. J. O.	R	41	M	W	21	None	20/20	N_2	3-19-68 6-14-68	Xenon do	9-16-68	6 months	20/20—1	1	B	
	L	--	--	--		40	20/60—	N_1H_1	6-14-68	do		3 months	20/400	.6	H_2	

72. R. B	R	20	M		3	27	20/400—	H_2		None			20/400—		H_2
	L	--	--	--		None	20/25—3	N_1F_1	5–21–68	Xenon	7–18–68	2 months	20/25	1	B
73. M. G	R	38	M	N	25	37	20/50—	N_1F_1	4–30–68 7–12–68	Xenon	8– 2–68	3 months	20/50—2	1	F_1
	L	--	--	--		37	20/20	N_1F_1		None			20/20		N_1F_1
74. E. D	R	67	F		52	66	20/400—	H_2		None			20/400—		H_2
	L	--	--	--		65	20/70	F_1H_1	7–11–67 8– 8–67	Xenon	8– 8–67	1 month	20/70—2	1	F_1H_1
75. E. R	R	43	F	W	12	31	20/25—	B		None	11–29–67		20/20—3		B
	L	--	--	--		31	20/30	N_1F_1	7–25–67	Xenon		4 months	20/30—2	1	N_1F_1
76. L. K	R	55	M	W	38	54	20/30	N_1H_1	4–11–67	Xenon	6–15–67	2 months	20/40—	.5	N_2
	L	--	--	--		51	20/200	F_1H_1		None			20/200—1		F_2
77. L. L	R	50	F	W	30	50	20/20—2	N_1	3–10–67	Xenon	7–29–68	16 months	20/400—	.9	H_2
	L	--	--	--		48	20/400—	H_2	7– 7–67	None			20/400—		H_2
78. J. O	R	59	M	W	34	59	20/25—	F_1	12–15–67	Xenon	2– 6–68	2 months	20/400—	.7	H_2
	L	--	--	--		55	20/400—	H_2		None			20/400—		H_2
79. S. E	R	42	F	W	18	41	20/400	H_2		None			20/400		H_2
	L	--	--	--		None	20/25	N_2	7–15–68	Xenon	9–27–68	5 weeks	20/25	1	B
80. R. J	R	39	F	W	15	37	20/100	B	5–15–66	Pituitary	6–15–68	2 months	20/50—	1	B
	L	--	--	--		38	20/70	B		T.C.			20/50—	1	B

[1] Degree of pituitary ablation: complete 1–22–68.
[2] Degree of pituitary ablation: Complete neurosurgery (transsection of stalk) resulted in damage to right optic nerve. Laser resulted in submacular hemorrhage lasting 3 months.
NB: This pt. is the 1st here to develop beginning thyrotoxicosis 1 year after pitutary ablation.
[3] Improvement OD due to resolution of vitreous hemorrhage.

Appendix N

P. C. WETZIG AND C. N. JEPSON

(DATA FROM CHAPTER 49)

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date and mode of therapy
1. R. A.	R	62	M	W	56	58	20/25	BH_0	7-2-62, 7-29-64, 4-21-66, LC.
	L	62	--	--	--------	58	20/70	BH_0	1-4-62, LC
2. R. A.	R	40	M	W	19	35	20/100	$N_2F_0H_1$	11-14-66, 5-6-67, 12-8-67, LC.
	L	40	--	--	--------	35	LP	H_2	11-22-66, 5-10-67, LC.
3. M. A.	R	24	M	W	13	22	20/30	N_2H_1	6-3-64, 9-13-64, 3-5-65, LC.
	L	--	--	--	--------	22	CF 4′	H_2	----------
4. J. A.	R	--	M	W	14	35	LP	----------	----------
	L	39	--	--	--------	35	20/20	$N_2F_1H_0$	8-23-66, 1-31-67, LC.
5. M. A.	R	65	F	W	43	63	20/400	H_2	8-28-65, LC
	L	--	--	--	--------	63	20/400	----------	----------
6. A. A.	R	31	F	W	6	30	20/40	F_2H_1	7-27-67, LC
	L	32	--	--	--------	29	LP	F_2H_1	5-29-68, LC
7. P. B.	R	--	M	W	--------	54	Anophthalmos	----------	----------
	L	56	--	--	--------	56	20/50	$BN_2F_2H_1$	3-5-66, 5-16-66, LC.
8. B. B.	R	41	F	W	19	39	20/30	N_1H_0	10-9-63, LC
	L	40	--	--	--------	39	20/40	N_1H_0	3-19-62, 10-19-63, 3-18-68, LC.
9. C. B.	R	65	F	W	37	66	CF 3′	BH_1	5-19-67, LC
	L	65	--	--	--------	66	CF 3′	BH_1	5-24-67, 9-6-67, LC.
10. M. B.	R	--	F	W	58	58	NLP	----------	----------
	L	75	--	--	--------	68	20/80	$N_1F_1H_1$	2-15-62, 5-3-62, LC.
11. F. B.	R	64	F	W	39	59	HM	H_2	4-14-67, 6-30-67, LC.
	L	--	--	--	--------	56	LP	----------	----------
12. D. B.	R	--	M	W	51	53	CF 3′	----------	----------
	L	54	--	--	--------	53	20/50	$BN_2F_2H_1$	5-24-66, LC
13. I. B.	R	43	M	W	29	38	HM 3′	N_2H_1	6-1-67, 6-22-67, LC
	L	43	--	--	--------	38	20/400	N_2H_1	6-12-67, 10-5-67, 10-7-67, LC.
14. L. B.	R	75	M	W	57	66	HM 1′	H_2	6-19-67, LC
	L	75	--	--	--------	66	3/300	H_2	4-13-67, 4-18-67, 6-9-67, LC.
15. C. B.	R	37	F	W	20	37	20/25	N_2H_1	4-21-66, 10-26-66, LC.
	L	37	--	--	--------	37	20/25	N_2H_1	4-19-66, 10-21-66, LC.
16. D. B.	R	24	M	W	14	24	20/25	B	11-24-64, 7-20-65, 11-16-65, LC.
	L	--	--	--	--------	24	LP	F_2H_2	11-24-64, LC
17. G. B.	R	59	M	W	55	59	20/80	BH_1	3-6-67, 8-3-67, LC
	L	59	--	--	--------	59	20/80	BH_1	3-15-67, LC
18. H. B.	R	50	M	W	27	41	10/300	B	4-20-60, 5-11-60, 6-17-60, 11-16-66, 12-6-67, 2-13-68, LC.
	L	50	--	--	--------	41	20/40	B	7-10-60, 12-5-60, 12-26-60, 5-6-64

See footnotes at end of table.

Date of last exam	Duration of followup	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Surgery	Complications	Cause of VA loss
6- 3-68	71 months	20/100	0.89	B			Cat.
6- 3-68	78 months	20/70	1	B			
12- 4-67	13 months	20/200	.31	$N_2F_0H_1$			Cat.
12- 4-67	13 months	LP	1	H_2			Cat.
1-31-67	31 months	20/30	1	F_1H_0			
1-31-67		20/30	1	B			
2- 6-68		LP					
2- 6-68	18 months	20/20	1	F_0H_0			
9- 7-65	2 weeks	20/400	1	H_2		(2)	
9- 7-65		20/400					
6-27-68	12 months	20/40	1	F_2H_1			
6-27-68	1 month	LP	1	F_2H_1	Cat. ext. 2-27-68.		Det. ret.
5-22-66	2 months	20/50	1	B			
4-16-68	54 months	20/30	1	N_1H_0			
4-16-68	73 months	20/30	1	F_1H_0			
9-11-67	4 months	20/400	1	BH_1			Mac. deg.
9-11-67	4 months	20/400	1	BH_1			Mac. deg., cat.
9-11-67		NLP					
5- 7-68	75 months	20/400	.64	H_0	Cat. ext.		Mac. deg.
7- 5-67	14 months	20/400	1	F_2			
7- 5-67		HM					
6- 1-66		CF 4′					
6- 1-66	7 days	20/100		(2)			
10-12-67	4 months	HM 1′	1	F_1H_1			
10-12-67	4 months	20/400	1	F_1H_1			
10-26-67	4 months	HM 1′	1	H_2			
10-26-67	6 months	3/300	1	H_2			
4-29-68	24 months	20/60	.46	BH_0			Cat.
4-29-68	24 months	20/40	.46	BH_0			Cat.
12- 2-67	37 months	20/25	1				
12- 2-67	37 months	20/400	1				
1-26-68	15 months	20/400	0	BH_1			Mac. spread.
1-26-68	15 months	20/70	1	BH_1			
6-24-68	98 months	20/400	1	F_1			
6-24-68	96 months	20/30	1	B			

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date and mode of therapy
19. P. B.	R	28	F	W	9	23	20/40	N_1H_0	11-23-66, LC
	L	26	--	--	--------	23	20/50	N_1H_0	4-29-64, 10-5-66, LC.
20. S. B.	R	26	F	W	4	26	20/25	N_2H_1	9-22-67, 1-12-68, 3-8-68, 4-26-68.
	L	26	--	--	--------	26	20/30	N_2H_1	9-25-67, 11-27-67, 4-29-68, LC.
21. M. B.	R	--	F	W	21	40	20/70	----------	----------
	L	42	--	--	--------	40	20/200	N_2H_1	1-31-63, LC
22. S. B.	R	64	M	W	56	62	20/200	B	10-5-67, LC
	L	64	--	--	--------	62	20/200	BN_1	10-2-67, LC
23. R. B.	R	19	M	W	3	18	LP	H_3	3-2 3-67, 4-25-67, LC.
	L	19	--	--	--------	18	20/30	N_2H_1	3-18-67, 3-29-67, 5-4-67, 5-10-67
24. R. B.	R	30	M	W	20	30	20/20	$BN_2F_1H_0$	8-18-67, 5-22-67, LC.
	L	--	--	--	--------	30	LP	----------	----------
25. R. B.	R	69	F	W	51	66	20/60	BH_1	8-1-62, 9-20-62, 3-20-63, LC
	L	69	--	--	--------	66	20/60	BH_1	12-20-62, LC
26. J. B.	R	63	F	W	45	45	20/25	F_1H_1	1-27-67, 6-14-67, LC.
	L	63	--	--	--------	45	20/30	F_1H_1	1-25-67 LC
27. C. C.	R	32	M	W	5	30	20/70	N_2H_1	10-10-67. 7-15-68, LC
	L	32	--	--	--------	30	20/40	B	10-3-67, 2-19-68, LC.
28. D. C.	R	30	M	W	9	26	CF 3′	$N_2F_2H_1$	8-19-64, 7-28-65, 12-8-65, 2-28-66, 10-18-66, 12-13-66, 2-23-67,
	L	30	--	--	--------	26	20/70	$N_2F_2H_1$	8-19-64, 7-29-65, 12-13-66, 2-22-67, 6-14-67
29. G. C.	R	65	M	W	50	65	20/200	$N_2F_1H_1$	2-13-68, LC
	L	65	--	--	--------	63	20/50	$N_2F_1H_1$	2-16-68, LC
30. I. C.	R	--	F	W	40	40	LP	H_2	----------
	L	60	--	--	--------	39	20/70	$N_2F_2H_1$	12-15-67, LC
31. M. C.	R	35	F	W	22	34	20/30	$N_2F_2H_1$	10-3-66, LC
	L	35	--	--	--------	34	20/50	$N_2F_2H_1$	9-23-66, 3-15-67, LC.
32. S. C.	R	Dec.	F	W	--------	--------	20/30	----------	4-23-68, LC
	L	--	--	--	--------	--------	LP	----------	4-26-68, LC
33. L. C.	R	56	F	W	41	55	20/100	$N_2F_2H_1$	10-13-66, LC
	L	56	--	--	--------	55	20/20	N_2H_1	9-28-66, 6-30-67, LC.
34. J. C.	R	--	M	W	12	33	Anophthalmos	----------	----------
	L	40	--	--	--------	35	20/20	$N_3F_3H_1$	12-1-65, 1-24-67, LC.
35. D. C.	R	19	F	W	6	18	20/20	BN_2H_0	8-6-66, LC
	L	19	--	--	--------	18	20/30	$BN_2F_0H_1$	8-3-66, LC
36. N. C.	R	46	F	W	23	46	HM 2′	H_2	5-6-66, 10-13-66, 10-3-67, LC
	L	46	--	--	--------	41	20/50	$N_2F_1H_1$	5-4-66, 6-20-66, 1-12-67, LC
37. C. C.	R	66	M	W	46	62	20/200	BH_1	9-12-67, LC
	L	66	--	--	--------	62	20/40	BH_1	9-14-67, LC
38. A. C.	R	65	M	W	54	64	20/50	B	6-26-68, LC
	L	--	--	--	--------	64	20/100	----------	----------

See footnotes at end of table.

C. N. JEPSON—Continued

Date of last exam	Duration of followup	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Surgery	Complications	Cause of VA loss
5-24-68	18 months	20/25	1	B			
5-24-68	18 months	20/25	1	B			
5-31-68	8 months	20/400	.33	$N_1F_2H_1$			Prog. of retin.
5-31-68	8 months	20/70	.33	$N_1F_2H_1$			Prog. of retin.
4- 8-64		20/80					
4- 8-64	15 months	20/40	1	N_1H_1			
7-10-68	8 months	20/200	1	B			
7-10-68	8 months	20/200	1	B			
5-10-67	2 months	LP	1	N_2F_2			Prog. of retin.
5-10-67	2 months	LP	1	$N_2F_2H_1$			Prog. of retin.
3-8-68	19 months	20/20	1				
3-8-68		LP					
5-13-68	69 months	20/40	1	B			
5-13-68	65 months	20/30	1	B			
6-14-68	17 months	20/25	1	N_2H_1			
6-14-68	17 months	20/30	1	N_2H_1			
7-17-68	8 months	20/60	1	F_1H_1			
7-17-68	8 months	20/30	1	B			
3-4-68	43 months	20/50	1	F_1H_1			
3-4-68	43 months	20/50	1	F_1H_1			
6-4-68	4 months	HM 2′	0	$N_2F_2H_1$			Prog. of retin.
6-4-68	4 months	CF 5′	0	$N_2F_2H_1$			Prog. of retin.
12-19-67		LP		H_2			
12-19-67	4 days			(2)			
3-17-67	5 months	20/30	1	F_2H_1			
3-17-67	6 months	20/40	1	F_2H_1		Branch vein occlusion	
4-28-68	1 week	(2)		(3)			
4-28-68	2 days	(2)					
7-5-67	9 months	HM 1′	0	$N_2F_2H_1$	Det. ret	Glaucoma, det. ret.	Glaucoma.
7-5-67	10 months	20/80	.14	F_1H_1			Macular pucker.
8- 7-67	20 months	20/20	1	F_1H_1			
1-18-67	6 months	20/20	1	B			
1-18-67	6 months	20/25	1	B			
4-20-68	23 months	HM 1′	1	H_1			Prog. of retin.
4-20-68	23 months	20/400	.2	N_1F_2	Det. ret		Prog. of retin.
9-16-67	4 days	20/200		(2)			
9-16-67	2 days	20/40		(2)			
6-26-68		20/25	1	B	Cat. ext. 1-16-68.		
6-26-68		20/100			Cat. ext. 9-19-67.		

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date and mode of therapy
39. G. C.	R	49	F	W	(1)	47	LP	H_2	7-8-67, 6-5-68, LC.
	L	49	--	--		47	LP	H_2	7-10-67, LC.
40. G. C.	R	39	M	W	22	38	20/40	$N_2F_1H_1$	6-14-67, 9-26-67, LC.
	L	39	--	--		38	LP	H_2	7-26-67, 7-29-67, LC.
41. C. C.	R	47	M	W	37	47	20/400	$N_2F_2H_1$	8-21-62, 2-11-63, LC.
	L	47	--	--		47	20/30	B	8-21-62, 10-12-62, 6-3-63, 8-16-65.
42. R. C.	R	36	F	W	6	36	20/25	$N_2F_1H_1$	4-13-66, LC.
	L	36	--	--		36	20/20	$N_2F_1H_1$	2-25-66, LC.
43. M. C.	R	57	F	W	48	55	LP	H_2	1-26-66, LC.
	L	56	--	--		56	20/20	$N_2F_2H_1$	12-14-65, 3-17-66, 12-7-66, 5-10-67, 6-28-67.
44. A. C.	R	65	F	W	58	64	20/400	$BN_2F_0H_0$	5-24-65, LC.
	L	--	--	--		64	Blind		
45. J. C.	R	41	F	W	11	40	20/50	H_2	4-4-65, 5-8-65, LC.
	L	41	--	--		40	CF 10′	H_2	4-17-65, LC.
46. M. C.	R	--	F	W	17	30	LP		
	L	32	--	--		30	20/40	$N_2F_2H_1$	9-22-66 LC.
47. R. C.	R	34	M	W	12	33	20/30	B	3-2-66 LC.
	L	34	--	--		33	20/400	B	2-16-66, 4-12-66, 4-26-66, 10-26-66.
48. D. C.	R	32	F	W	20	28	20/100	$N_2F_1H_1$	11-18-60, 12-16-60, 3-30-62, 12-12-62.
	L	33	--	--		28	20/70	$N_2F_1H_1$	3-3-61, 5-27-61, 6-16-61, 4-29-68.
49. W. C.	R	62	M	W	54	54	20/25	B	1-16-64 LC.
	L	--	--	--		54	20/25		
50. E. C.	R	29	M	W	6	28	20/50	$N_2F_1H_1$	1-11-67 LC.
	L	29	--	--		28	20/40	$N_2F_1H_1$	1-13-67, 4-24-68 LC.
51. M. C.	R	24	F	W	8	24	20/70	$BN_2F_2H_1D$	12-19-66 LC.
	L	24	--	--		24	20/20	$BN_1F_1H_1$	12-22-66 LC.
52. J. D.	R	42	M	W	10	42	20/70	$N_2F_2H_1$	6-8-66, 11-4-66 LC.
	L	42	--	--		41	20/40	$N_2F_2H_1$	6-11-66, 11-16-66, 4-30-68, 5-6-68.
53. M. D.	R	67	F	W	56	67	20/25	$N_1F_1H_0$	8-30-66 LC.
	L	--	--	--		67	20/30		
54. M. D.	R	44	F	W	41	44	CF 3′		10-21-66 LC.
	L	44	--	--		44	CF 3′		10-25-66 LC.
55. E. D.	R	61	F	W	47	59	20/100	N_2H_1	5-22-62, 12-26-62, 8-26-64, 9-9-65.
	L	66	--	--		59	20/70	B	4-17-67, LC.
56. R. D.	R	50	F	W	(1)	50	20/50	$N_1F_1H_1$	3-20-67, LC.
	L	50	--	--		50	20/20	$N_1F_1H_1$	5-22-67, LC.
57. D. D.	R	62	M	W	(1)	56	LP	F_2	7-21-62, LC.
	L	62	--	--		56	20/70	$N_2F_2H_1$	2-13-62, 4-23-62, 5-12-62, LC.
58. B. D.	R	34	M	W	6	34	20/30	$N_2F_2H_1$	9-25-65, 5-14-66, LC.
	L	--	--	--		33	LP		
59. J. D.	R	38	F	W	18	37	20/70	N_2H_1	1-24-68, LC.
	L	38	--	--		38	20/70	N_2H_1	1-29-68, LC.
60. I. D.	R	61	F	W	41	61	3/300	H_2	5-31-67, 8-2-67, LC.
	L	61	--	--		61	20/40	$N_2F_2H_1$	5-29-67, 6-26-68, LC.

See footnotes at end of table.

C. N. JEPSON—Continued

Date of last exam	Duration of followup	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Surgery	Complications	Cause of VA loss
6- 5-68	11 months	LP	1	H_2			
6- 5-68	11 months	LP	1	H_2			
11- 3-67	5 months	20/300	.25	$N_2F_2H_1$		Det. ret	Prog. of retin.
11- 3-67	4 months	LP	1	H_2		Det. ret	Prog. of retin.
7-31-67	59 months	HM	0	$N_2F_2H_1$			Prog. of retin.
7-31-67	59 months	20/25	1	B			Prog. of retin.
6-30-68	24 months	20/25	1	B			
6-30-68	26 months	20/25	1	B			
10- 8-67	21 months	CF 3′	1	H_2			Prog. of retin.
10- 8-67	22 months	NLP	.17	$N_2F_1H_1$		Glaucoma	Prog. of retin.
5-27-68	36 months	CF 3′	.18	H_2		Vitreous hem	Mac. hole.
5-27-68		Blind					Rubeosis iridis.
5-17-65	1 month	20/50	1	$N_2F_2H_1$			
5-17-65	1 month	20/60	1	$N_2F_2H_1$			
8-22-67							
8-22-67	11 months	20/40	1	F_1H_1			
4-18-68	25 months	20/20	1	B			
4-18-68	26 months	20/200	1	B			
6- 6-68	91 months	20/40	1	F_1	Cat. ext. 2-7-58.		
6- 6-68	87 months	20/80	1	F_1	Cat. ext. 3-9-61.		
7-12-65	18 months	20/30	1	B			
7-12-65		20/25					
5-29 68	16 months	HM	0	H_2		Vitreous hem	Vitreous hem.
5-29-68	16 months	20/60	.9	$N_1F_2H_1$			
3-24-67	4 months	20/400	0	$BN_2F_2H_1D$			Det. ret.
3-24-67	4 months	20/20	1	B			
5- 6-68	23 months	LP	0	H_2		Det. ret	Prog. of retin.
5- 6-68	23 months	LP	0	H_2			Prog. of retin.
11-30-66	4 months	20/25	1	$N_1F_1H_0$			
11-30-66		20/30					
10-28-66	7 days	CF 3′	1	(2)			
10-28 66	3 days	CF 3′	1	(2)			
4-26-68	71 months	3/300	.21	BH_1			Prog. of retin.
4-26-68	12 months	20/200	0	F_1			Prog. of retin.
4-22-68	13 months	20/40	1	BH_0			
4-22-68	11 months	20/30	.82	BH_0			Cat.
10-21-66	51 months	LP	1	F_2	Cat. ext. 3-13-62.		
10-21-66	56 months	20/50	1	F_0			
3- 4-68	30 months	20/25	1	F_2H_1			
3- 4-68		LP					
2- 3-68	1 month	(2)		N_2H_1			
2- 3-68	1 month	(2)		N_2H_1			
6-28-68	13 months	20/60	1	$N_1F_2H_1$			
6-28-68	13 months	20/50	.15	$N_1F_2H_1$			Macular exudates.

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date and mode of therapy
61. D. D.	R	67	M	W	22	64	5/300	$N_2F_1H_1$	3-7-67, LC.
	L	67	--	--	--	64	20/50	N_1	7-12-67, LC.
62. P. D.	R	36	M	W	(1)	35	20/20	N_2F_1	11-22-66, 3-10-67, 3-21-67, LC.
	L	37	--	--	--	35	5/300	H_2	3-15-67, LC.
63. C. D.	R	27	F	W	10	25	HM 1′	H_2	12-6-66, 4-14-67, 10-3-67, LC.
	L	27	--	--	--	25	20/70	$N_2F_2H_1$	11-29-66, 4-11-67, 4-17-67, 10-9-67.
64. L. D.	R	41	F	W	20	40	20/200	B	8-10-66, LC.
	L	41	--	--	--	40	20/200	B	8-13-66, LC.
65. M. E.	R	37	M	W	12	32	20/40	$N_2F_2H_1$	5-14-64, LC.
	L	--	--	--	--	32	3/300	----------	----------
66. J. E.	R	67	M	W	37	67	20/400	$N_2F_2H_2$	9-22-65, LC.
	L	67	--	--	--	67	LP	F_2	9-23-65, LC.
67. C. E.	R	69	M	W	49	68	HM 1′	H_2	2-28-68, LC.
	L	69	--	--	--	68	3/300	H_2	3-2-68, LC.
68. B. E.	R	76	F	W	51	73	20/50	$N_2F_2H_1$	1-4-61, 2-16-61, 7-6-61, LC.
	L	--	--	--	--	68	20/40	----------	----------
69. B. E.	R	--	F	W	46	68	20/300	----------	----------
	L	66	--	--	--	66	HM	$N_2F_2H_1$	6-29-60, 7-14-60, 8-9-60, 12-8-60, 1-5-61.
70. M. E.	R	62	F	W	24	57	20/25	B	8-31-66 LC.
	L	--	--	--	--	57	20/25	----------	----------
71. J. F.	R	70	M	W	50	66	20/200	B	5-21-63, 2-19-64, LC.
	L	70	--	--	--	69	20/50	B	5-21-63, 4-21-64, LC.
72. A. F.	R	--	F	W	39	53	LP	----------	----------
	L	54	--	--	--	54	3/300	H_2	6-1-67, LC.
73. F. F.	R	35	M	W	4	24	20/200	$BN_2F_2H_1$	7-25-66, LC.
	L	35	--	--	--	24	20/25	$BN_2F_1H_0$	7-29-66, LC.
74. I. F.	R	66	F	W	26	58	CF 3′	BF_2H_0	2-2-68, LC.
	L	66	--	--	--	61	20/40	BF_1H_0	2-5-68, LC.
75. F. F.	R	56	F	W	24	56	20/70	B	6-15-62, 11-30-63, 4-11-64, 5-18-64.
	L	56	--	--	--	56	20/100	$N_2F_2H_1$	5-12-62, 6-20-62, 6-26-63, 10-8-64.
76. F. F.	R	--	M	W	74	74	CF 3	----------	----------
	L	74	--	--	--	73	20/100	BF_0H_0	12-3-65, LC.
77. P. F.	R	30	M	W	5	30	20/25	N_1	7-21-65, LC.
	L	30	--	--	--	30	20/50	N_1	7-18-65, 8-25-65, LC.
78. G. F.	R	44	M	W	18	43	20/20	N_1	8-25-66, LC.
	L	44	--	--	--	39	20/70	N_2F_2	8-22-66, 12-8-66, 5-24-67, 11-8-67, 5-9-68.
79. N. F.	R	29	M	W	11	29	20/20	B	11-16-66, 9-22-67, LC.
	L	29	--	--	--	29	20/20	B	11-19-66, LC.

See footnotes at end of table.

C. N. JEPSON—Continued

Date of last exam	Duration of followup	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Surgery	Complications	Cause of VA loss
4–24–68	13 months	HM 2′	0	N_1F_1			Prog. of retin.
4–24–68	9 months	20/40	1	N_1F_1			
3–31–67	5 months	20/20	1	F_2H_1			
3–31–67	3 weeks	20/100	1	F_2H_1			
4–22–68	16 months	20/400	1	F_2H_1			
4–22–68	17 months	20/200	.9	F_2H_1			
9–19–66	2 months	20/200	1	B			Mac. deg., cat.
9–19–66	2 months	20/200	1	B			Cat.
8–17–64	3 months	20/40	1	F_1			
8–17–64		LP			Cat. ext. 2–13–64.		
6–28–67	21 months	3/300	0	F_2			Prog. of retin.
6–28–67	21 months	NLP	0	F_2			Cat.
5–24–68	3 months	HM 1′	1	H_2		Keratitis, iritis	
5–24–68	2 months	2/300	0	H_2		Keratitis, iritis	Vit. Hem.
10– 1–63	34 months	NLP	.24	$N_1F_2H_1$	Cat. ext. 7–26–62.		Rubeosis iridis.
10– 1–63		20/40			Cat. ext. 5–24–60.		
1–10–62		20/300					
1–10–62	18 months	LP	.77	$N_1F_2H_1$	Det. ret. 5–26–61.	Det. ret	
5– 7–68	23 months	20/20	1	B			
5– 7–68		20/40					
5–16–66	36 months	20/400	.41	B			Cat.
5–16–66	36 months	20/100	.72	B			Mac. deg.
6–24–68		LP			Cat. ext. 5–9–68.		
6–24–68	12 months	HM	.5	F_2	Cat. ext. 5–14–68.	Keratitis	
6–14–68	23 months	20/100	1	$BN_2F_2H_1$			
6–14–68	23 months	20/20	1	F_1			
5–29–68	3 months	CF 3′	1	BF_2H_0			
5–29–68	3 months	20/25	1	F_1			
5–14–68	71 months	20/50	1	F_1			
5–14–68	72 months	NLP	.34	F_2		Vitreous Hem.	Rubeosis of iris, prog. of retin.
3–14–67		20/400					
3–14–67	15 months	20/100	1	BF_0H_0			Mac. deg.
8–25–65	1 month			(2)			
8–25–65	1 month			(2)			
5–10–68	21 months	20/20	1	N_1			
5–10–68	21 months	20/200	.43	F_2H_1			Prog. of retin.
9–22–67	10 months	20/20	1	B			
9–22–67	10 months	20/20	1	B			

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date and mode of therapy
80. M. F.	R	35	F	W	14	35	20/30	$N_2F_2H_1$	3-1-65, 7-17-65, 4-12-66, LC.
	L	35	--	--	--------	34	HM 1′	$N_2F_2H_1$	2-11-65, LC
81. D. F.	R	39	M	W	21	38	20/200	$N_2F_2H_1$	1-4-62, 2-15-62, 6-14-62, LC.
	L	39	--	--	--------	39	20/30	$N_2F_2H_1$	1-8-62, 3-1-62, 6-21-62, LC.
82. S. F.	R	39	F	W	13	39	3/300	B	1-3-68, LC
	L	39	--	--	--------	39	20/50	B	1-17-68, LC
83. A. G.	R	29	F	W	(1)	26	20/50	$N_2F_2H_1$	10-13-65, LC
	L	--	--	--	--------	26	20/25	----------	----------
84. G. G.	R	50	F	W	27	50	20/30	$N_2F_2H_1$	6-7-66, LC
	L	50	--	--	--------	49	LP	H_2	6-15-66, LC
85. H. G.	R	70	M	W	50	69	20/100	$N_2F_2H_1$	11-11-64, 7-22-65, 4-6-66, LC.
	L	70	--	--	--------	68	CF 5′	$N_2F_2H_1$	11-8-64, 3-1-65, 8-30-65, 12-21-66, 6-16-67.
86. S. G.	R	53	M	W	29	43	20/30	BF_2H_0	8-7-67, LC
	L	53	--	--	--------	43	20/30	BF_2H_0	8-4-67, 10-10-67, LC.
87. B. G.	R	58	F	W	52	51	5/300	N_2F_2	1-11-64, 3-12-64, LC.
	L	61	--	--	--------	54	5/300	$N_2F_2H_1$	8-8-67, 1-11-68, LC.
88. B. G.	R	--	F	W	(1)	29	3/300	----------	----------
	L	29	--	--	--------	29	20/400	$N_2F_2H_1$	11-23-66, LC
89. H. G.	R	49	M	W	43	45	20/30	$N_2F_1H_1$	12-30-64, 2-24-65, LC.
	L	49	--	--	--------	43	20/400	$N_2F_2H_1$	12-10-64, 6-9-65, 2-17-66, LC.
90. D. G.	R	36	M	W	11	27	20/200	$N_2F_2H_1$	2-9-61, 4-13-61, 6-6-61, LC.
	L	--	--	--	--------	27	20/100	----------	----------
91. R. G.	R	35	M	W	17	34	20/40	$N_2F_1H_1$	1-10-67, 2-19-67, LC.
	L	35	--	--	--------	34	20/70	$N_2F_1H_1$	1-12-67, 2-23-67, LC.
92. W. H.	R	--	M	W	6	--------	Anophthalmos.	----------	----------
	L	--	--	--	--------	24	HM	$N_2F_2H_1$	4-6-66, LC and det. ret.
93. M. H.	R	25	F	W	(1)	21	20/100	N_1F_2	12-30-67, LC
	L	25	--	--	--------	21	LP	N_2F_2	1-28-37, LC
94. D. H.	R	--	--	--	--------	--------	20/50	$N_2F_1H_1$	11-9-67, 2-5-68, 6-13-68, LC.
	L	--	--	--	--------	--------	20/30	$N_2F_1H_1$	11-7-67, 2-7-68, LC.
95. D. H.	R	29	F	W	9	27	20/30	$N_1F_2H_1$	1-7-67, 7-11-67, LC.
	L	28	--	--	--------	27	20/50	$N_2F_1H_1$	12-29-66, 7-7-67, LC.
96. P. H.	R	28	M	W	4	28	20/25	$N_2F_1H_1$	6-14-66, LC
	L	28	--	--	--------	28	20/25	$N_2F_1H_1$	6-18-66, LC
97. W. H.	R	--	M	W	12	27	20/50	----------	----------
	L	30	--	--	--------	27	20/200	$N_2F_1H_1$	6-1-67, LC
98. E. H.	R	27	M	W	14	24	20/20	$N_2F_0H_1$	3-2-62, 4-23-62, LC.
	L	26	--	--	--------	23	20/20	$N_2F_0H_1$	11-31-61, 1-19-62, 5-8-62, LC.

See footnotes at end of table.

C. N. JEPSON—Continued

Date of last exam	Duration of followup	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Surgery	Complications	Cause of VA loss
5–11–68	38 months	LP	0	$N_2F_2H_1$	Det. ret. 1–6–66.		Det. ret.
5–11–68	39 months	NLP	0	$N_2F_2H_1$	Det. ret. 1–13–66.		Det. ret.
3– 5–68	74 months	NLP	.1	$N_2F_2H_1$	Det. ret., LC 3–22–62.	Det. ret	Rubeosis, iritis.
3– 5–68	74 months	NLP	0	$N_2F_2H_1$		Det. ret	Rubeosis, iritis.
1–26–68	3 weeks	3/300	1	B			
1–26–68	3 weeks	20/40	1	B			
1–18–66	3 months	4/300	0	$N_1F_2H_1$			Prog of retin.
1–18–66		20/40					
11–13–67	17 months	20/30	1	F_1			
11–13–67	17 months	LP	1	H_2			
5–29–68	42 months	LP	0	H_2		Vit. hem	Rubeosis, iritis, glaucoma.
5–29–68	42 months	20/50	1	F_2H_1			
7– 5–68	11 months	20/30	1	F_1			
7– 5–68	11 months	20/30	1	F_1			Cat.
6– 7–68	53 months	3/300	1	F_1			Cat.
6– 7–68	10 months	5/300	1	F_1			
12–14–66		CF 4′					
12–14–66	1 month	20/100	1	$N_1F_1H_1$			
4–18–68	41 months	20/20	1	F_1			
4–18–68	41 months	20/100	1	F_1			
7–21–61	5 months	20/600	.6	N_1F_1			Mac. cyst.
7–21–61		20/70					
5–29–67	4 months	20/300	0	$N_2F_1H_1$			Prog. of retin.
5–29–67	4 months	20/400	0	$N_2F_1H_1$			Prog. of retin.
6–24–68	26 months	LP	0	$N_2F_2H_1$	Det. ret		Prog. of retin.
3–25–68	3 months	20/90	1	F_2			
3–25–68	2 months	LP	1	N_2F_2	Det. ret. 1–24–67.		
6–28–68	7 months	20/50	1	$N_2F_1H_1$			
6–28–68	7 months	20/30	1	$N_2F_1H_1$			
7–11–67	6 months	20/25	1	N_1F_2			
7–11–67	7 months	20/25	1	N_1F_2			
3–22–67	9 months	20/25	1	F_1			
3–22–67	9 months	20/20	1	F_1			
6–19–67		20/80					
6–19–67	2½ weeks	HM	0	N_1F_2			
5–23–62	2½ months	20/20	1	F_1			
5–23–62	6 months	20/20	1	F_1			

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date and mode of therapy
99. A. H.	R	62	M	W	21	61	20/30	$N_2F_2H_1$	6 28-67, 11-22-67, LC.
	L	62	--	--	--------	61	20/40	$N_2F_2H_1$	7-26-67, 2-13-68, LC.
100. L. H.	R	24	M	W	10	23	20/400	N_2H_1	9-26-66, LC
	L	24	--	--	--------	23	20/60	N_2H_1	10-4-66, 11-16-66, 1-10-67, LC.
101. E. H.	R	46	M	W	17	43	20/30	$BN_1F_1H_1$	1-22-68, LC
	L	46	--	--	--------	43	HM	H_2	1-26-68, LC
102. D. H.	R	47	M	W	26	47	20/30	N_1H_1	1-10-67, LC
	L	47	--	--	--------	47	20/30	N_1H_1	1-7-67, LC
103. I. H.	R	28	M	W	14	25	20/300	$N_2F_2H_1$	6-18-66, 8-23-66, 6-27-67, LC.
	L	29	--	--	--------	25	LP	H_2	7-5-67, 7-15-67, 12-22-67, 2-20-68, 5-29-68.
104. A. H.	R	66	F	W	42	60	20/80	----------	9-2-64, LC
	L	--	--	--	--------	58	Anoph thalmos.	----------	----------
105. E. H.	R	--	M	W	--------	--------	20/70	B	12-21-66, LC
	L	--	--	--	--------	--------	20/25	B	12-27-66, LC
106. J. B.	R	--	F	W	--------	--------	20/20	B	6-13-66, LC
	L	--	--	--	--------	--------	20/20	B	6-16-66, LC
107. A. I.	R	51	F	W	25	48	LP	H_2	3-21-68, 4-22-68, LC.
	L	51	--	--	--------	48	20/400	$N_2F_2H_1$	2-28-68, 4-18-68, LC.
108. J. J.	R	36	M	W	30	31	20/400	$N_2F_2H_1$	9-11-63, 1-20-64, LC.
	L	36	--	--	--------	31	20/20	N_2F_1	9-11-63, 10-9-63, 1-20-64, 10-28-64.
109. G. J.	R	29	M	W	9	29	5/300	H_2	1-26-68, LC
	L	27	--	--	--------	29	20/40	$N_2F_2H_1$	1-30-68, 5-7-68, 5-9-68, LC.
110. N. J.	R	52	F	W	34	49	20/50	$N_2F_2H_1$	12-16-66, 4-11-67, 7-12-68, 11-27-67, 3-4-67, 5-27-68.
	L	52	--	--	--------	48	20/200	$N_2F_2H_1$	12-14-66, 4-14-67, LC.
111. J. J.	R	51	M	W	45	48	20/200	$N_2F_2H_1$	4-17-65, 6-25-65, LC.
	L	51	--	--	--------	47	3/300	$N_2F_2H_1$	4-15-65, 6-26-65, LC.
112. R. J.	R	72	M	W	55	70	LP	H_2	7-29-67, 12-6-67, 2-21-68, LC.
	L	72	--	--	--------	70	20/30	B	7-26-67, LC
113. H. K.	R	66	M	W	46	64	LP	H_2	8-7-66, LC
	L	66	--	--	--------	64	20/25	$N_2F_1H_1$	9-14-66, 2-1-67, LC.
114. E. K.	R	38	F	W	17	35	HM 2′	H_2	3-22-67, 4-10-67, 7-25-67, LC.
	L	38	--	--	--------	35	20/30	$N_2F_2H_1$	3-15-67, 8-29-67, 7-18-67, LC.
115. E. K.	R	31	M	W	5	24	20/100	$N_2F_2H_1$	7-13-67, LC
	L	31	--	--	--------	24	20/30	$N_2F_2H_1$	7-17-67, LC
116. E. K.	R	48	F	W	9	31	20/400	$N_2F_1H_1$	11-22-67, LC
	L	--	--	--	--------	30	HMI	----------	----------
117. A. K.	R	--	M	W	23	46	20/30	----------	----------
	L	47	--	--	--------	47	20/25	$N_2F_1H_1$	7-12-67, LC
118. K. K.	R	63	F	W	55	62	20/20	BH_6F_0	4-13-68, LC
	L	63	----	--	--------	62	20/40	BH_0F_0	4-10-68, LC

See footnotes at end of table.

C. N. JEPSON—Continued

Date of last exam	Duration of followup	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Surgery	Complications	Cause of VA loss
5- 2-68	11 months	20/40+	.55	F_2H_1			Prog. of retin.
5- 2-68	10 months	20/60	0	F_2H_1			Vit. hem.
1-13-67	4 months	20/400	1	N_2H_1			Prog. of retin.
1-13-67	4 months	CF 3′	0	N_2H_1			Prog. of retin.
7- 8-68	6 months	20/30	1	H_2			
7- 8-68	6 months	CF 3′	1	H_2			
10-26-67	9 months	20/60	.4	F_1			Prog. of retin.
10-26-67	9 months	20/30	1	F_1			
6-24-68	24 months	20/400	.75	F_2H_1			Prog. of retin.
6-24-68	24 months	10/300	1	H_2			
9- 4-64	2 days	CF 5′	-------	(2)			
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4-19-67	5 months	20/70	1	B			
4-19-67	5 months	20/25	1	B			
12-24-66	6 months	20/20	1	B			
12-24-66	6 months	20/20	1	B			
6-30-68	3 months	CF 3′	1	H_2			
6-30-68	4 months	20/400	1	$N_2F_2H_1$		Det. ret	
1-26-68	63 months	20/200	1	F_2			
1-26-68	63 months	20/40	0	B		Mac. burn	Mac. burn.
5-11-68	5 months	LP	0	H_2			Prog. of retin.
5-11-68	5 months	20/400	0	$N_2F_2H_1$		Det. ret	Prog. of retin.
6- 3-68	18 months	20/400	.22	$N_1F_2H_1$			Prog. of retin.
6- 3-68	18 months	LP	0	N_2F_2	Det. ret. 5-28-68.	Det. ret	Prog. of retin.
6-28-65	2 months	LP	0	$N_2F_2H_1$			Prog of retin.
6-28-65	2 months	LP	0	$N_2F_2H_1$			Prog. of retin.
2-21-68	7 months	20/100	1	$N_2F_2H_1$			
2-21-68	7 months	20/30	1	B			
8- 7-67	12 months	20/400	1	H_2			
8- 7-67	12 months	20/40	.9	B			Mac. exudates.
7-15-68	16 months	HM 2′	1	F_2			
7-15-68	16 months	20/30	1	F_2			
7-17-67	4 days	-------	-------	(2)			
7-17-67	------	-------	-------	(2)			
6-21-68	7 months	20/400	1	F_2			
6-21-68	------	HMI	-------	------			
12-15-67	------	20/25	-------	------			
12-15-67	5 months	20/25	1	F_1			
6-30-68	2 months	20/20	1	BH_0F_0			
6-30-68	2 months	20/40	1	BH_0F_0			Cat.

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date and mode of therapy
119. R. K.	R	31	M	W	13	23	10/300	H_2	3-22-67, 8-7-67, 1-23-68, LC.
	L	31	--	--	--------	23	20/25	$N_2F_2H_1$	3-20-67, 1-25-68, 5-11-68, 6-25-68.
120. F. L.	R	--	F	W	23	43	HMN	----------	----------
	L	43	--	--	--------	42	20/400	H_2	7-2-62, LC
121. B. L.	R	51	F	W	27	51	LP	H_2	7-14-64, 9-11-64, 12-9-64, 6-22-66.
	L	51	--	--	--------	51	20/30	B	7-14-64 6-23-66, LC.
122. B. L.	R	29	M	W	15	28	20/25	N_2F_2	10-25-65, 6-21-66, 9-21-66, 3-15-67.
	L	31	--	--	--------	28	20/25	N_2F_2	10-23-67, 6-23-66, 3-18-67, LC.
123. C. L.	R	57	F	W	37	57	10/300	B	8-3-67, LC
	L	57	--	--	--------	55	20/25	B	7-31-67. LC
124. M. L.	R	27	M	W	12	25	20/70	$N_2F_2H_1$	2-25-65, 5-11-65, 1-21-66, LC.
	L	27	--	--	--------	26	20/30	$N_1F_1H_1$	2-29-65, 12-8-66, LC.
125. S. L.	R	24	F	W	2	20	20/25	$N_2F_2H_1$	4-12-67, 9-22-67, LC.
	L	24	--	--	--------	20	20/25	$N_2F_2H_1$	4-14-67, LC
126. B. L.	R	44	F	W	(1)	41	20/50	$N_2F_2H_1$	1-30-67, 5-23-67, LC.
	L	44	--	--	--------	42	20/30	N_2F_1	2-2-67, 5-26-67, LC.
127. L. L.	R	49	F	W	30	46	20/30	$N_2F_1H_1$	3-10-67, LC
	L	49	--	--	--------	45	LP	H_2	5-31-67, LC
128. S. L.	R	30	M	W	9	29	20/30	N_2F_1	6-21-67, 9-18-67, 9-21-67, LC.
	L	30	--	--	--------	29	20/100	$N_2F_2H_1$	6-24-67, 3-1-68, LC.
129. A. L.	R	52	F	W	34	51	HM 1'	H_2	11-14-66, LC
	L	52	--	--	--------	51	20/40	N_2H_1	9-17-66, 11-16-66, LC.
130. J. M.	R	45	M	W	25	43	20/25	N_1H_1	12-11-67, LC
	L	45	--	--	--------	43	20/400	$N_2F_2H_1$	12-8-67, LC
131. F. M.	R	69	F	W	25	66	CF 4'	BH_1	9-5-63, LC
	L	69	--	--	--------	69	20/400	BH_1	9-5-63, LC
132. B. M.	R	33	M	W	18	33	20/100	N_2H_2	11-2-66, 4-10-67, LC.
	L	33	--	--	--------	33	20/60	$N_2F_2H_1$	11-4-66, 4-14-67, LC.
133. B. M.	R	36	F	W	16	36	20/70	B	10-25-66, LC
	L	36	--	--	--------	36	20/100	$N_2F_2H_1$	11-2-66, LC
134. B. M.	R	43	F	W	21	36	20/40	N_2H_1	3-18-64, 5-6-64, 7-28-64, LC.
	L	43	--	--	--------	36	20/40	N_2H_1	10-28-64, 3-24-65, LC.
135. A. M.	R	79	M	W	(1)	78	20/40	----------	9-20-65, LC
	L	--	--	--	--------	78	LP	----------	----------
136. W. M.	R	33	M	W	8	32	20/400	$N_2F_2H_1$	7-20-67, 11-8-67, 2-7-68, LC.
	L	33	--	--	--------	33	3/300	H_2	7-25-67, 2-5-68, LC.
137. C. M.	R	--	F	W	11	34	HMT	----------	----------
	L	42	--	--	--------	37	20/50	N_1F_2	6-27-67, 10-11-67, LC.
138. J. M.	R	57	M	W	32	52	15/400	$N_2F_1H_1$	2-12-62, 9-27-62, LC.
	L	54	--	--	--------	52	20/80	$N_2F_1H_1$	10-26-59, 1-14-61, LC.

See footnotes at end of table.

C. N. JEPSON—Continued

Date of last exam	Duration of followup	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Surgery	Complications	Cause of VA loss
6-26-68	15 months	20/40	1	$N_2F_2H_1$			
6-26-68	15 months	20/80	.46	$N_2F_2H_1$		Det. ret	Det. ret.
7- 9-62		HMN					
7- 9-62	1 week			(2)			Cat.
3- 4-68	44 months	20/40	1	F_1		Mac. burn	
3- 4-68	44 months	20/20	1	B			
3-20-67	17 months	20/20	1	B			
3-20-67	17 months	20/20	1	B			
2-28-68	6 months	10/300	1	B			
2-28-68	7 months	20/20	1	B			
12-12-66	22 months	20/30	1	F_1			
12-12-66	22 months	20/30	1	F_1			
2-29-68	10 months	20/25	1	F_1			
2-29-68	10 months	20/25	1	F_1			
3-25-68	14 months	HM	.2	N_1F_1			Vitreous hemorrhage.
3-25-68	13 months	20/20	1	F_1			
7-22-68	16 months	20/20	1	F_1			
7-22-68	16 months	NLP	0	H_2		Keratitis	Rubeosis, iritis, glaucoma.
3- 2-68	9 months	0/25	1	N_1F_1			
3- 2-68	9 months	HM	0	N_2F_2			Prog. of retin.
11-28-66	2 weeks	HM 1′	1	H_2			
11-28-66	2 months	20/40	1	N_1			
6-30-68	6 months	20/20	1	F_1			
6-30-68	6 months	HM 3′	0	$N_2F_2H_1$	Det. ret. 7-26-68.	Det. ret	Prog. of ret. det. retina.
10-14-63	3 weeks	CF 4′	1	(2)			Cat.
10-14-63	3 weeks	CF 3′		(2)			Cat.
12- 4-67	13 months	20/40	1	N_1F_1			
12- 4-67	13 months	20/400	0	H_2			Vitreous hem.
3-23-67	5 months	20/70	1	B			
3-23-67	4 months	20/100	1	$N_1F_2H_1$			
8-20-65	17 months	20/40	1	N_1F_2			
8-20-65	10 months	20/30	1	N_1F_2			
9-27-65	7 days	20/40	1	(2)			
9-27-65		LP					
3- 6-68	8 months	HM 1′	.35	$N_2F_2H_1$			Vitreous hem.
3- 6-68	8 months	HM 1′	.35	H_2			Vitreous hem.
2-19-68		HMT					
2-19-68	8 months	20/50	1	F_2			
6-17-66	50 months	HM	.14	F_2	Cat. ext. 6-16-65.		Prog. of retin.
6-17-66	80 months	LP	.29	F_2	Cat. ext. 1-26-66.		Prog. of retin.

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date and mode of therapy
139. M. M.	R	23	F	W	9	22	20/150	$N_2F_1H_1$	6-8-66, 11-22-66, LC.
	L	23	--	--	--	22	20/70	$N_2F_1H_1$	6-1-66, LC
140. V. M.	R	40	M	W	12	37	3/300	$N_2F_2H_1$	7-20-60, 9-20-60, 3-2-61, 12-19-61, 4-3-62, 10-4-62, 10-8-64, LE.
	L	41	--	--	--	37	20/70	$N_2F_1H_1$	9-13-60, 9-20-60, 8-8-61, 12-18-62, 5-28-63, 9-14-63
141. S. M.	R	62	F	W	55	61	20/50	N_1F_2	6-21-67 LC
	L	--	--	--	--	58	HMT		
142. M. M.	R	19	M	W	6	18	20/40	$N_2F_1H_1$	6-8-66, 8-25-66, 1-23-67, LC.
	L	19	--	--	--	18	20/50	$N_2F_1H_1$	6-11-66, 8-23-66, 1-13-67, LC.
143. M. M.	R	53	F	W	18	45	20/200	$N_2F_1H_1$	3-24-65, 3-4-65, 1-12-66, 4-27-66, 6-22-66, 8-24-66, 5-1-66.
	L	53	--	--	--	45	20/40	$N_1F_1H_1$	5-6-65, 10-5-66, 5-11-67, 8-2-67, 8-25-67.
144. J. M.	R	32	M	W	15	30	20/20		3-4-68, LC
	L	32	--	--	--	30	20/25		3-6-68, LC
145. J. M.	R	32	M	W	13	31	2/300	$N_2F_2H_1$	2-22-68, LC
	L	32	--	--	--	31	20/25	$N_2F_2H_0$	2-26-68, LC
146. O. M.	R	23	F	W	7	21	20/30	N_1H_1	4-21-60, 4-28-60, 5-5-60, LC.
	L	--	--	--	--	21	20/25	N_1H_0	6-9-60, 5-19-60 LC
147. F. M.	R	79	F	W	69	79	20/400	B, mac. deg.	8-19-65 ,LC
	L	79	--	--	--	79	20/400	B, mac. deg.	10-11-65, LC
148 E. M.	R	50	F	W	26	50	20/40	N_2H_1	3-17-64, 4-29-64, 7-13-65, 9-21-66.
	L	50	--	--	--	50	20/200	H_2	4-14-64, 8-26-64, 10-14-64, 6-24-65.
149. A. M.	R	46	M	W	25	45	20/20	B	6-1-66. LC
	L	45	--	--	--	45	20/20	B	8-18-65, 6-5-68, LC.
150. B. M.	R	29	M	W	12	27	20/80	$BN_2F_2H_1$	2-14-67, LC
	L	29	--	--	--	29	20/20	$BN_2F_2H_1$	2-11-67, 7-22-67, LC.
151. J. N.	R	56	F	W	21	55	LP		7-29-67, LC
	L	56	--	--	--	55	LP		7-1-67, LC
152. K. N.	R	48	M	W	33	47	20/50	N_1H_0	10-1-63, LC
	L	48	--	--	--	47	20/400	N_1H_0	10-1-63, 1-22-64, 2-23-66, LC
153. K. N.	R	68	F	W	52	66	20/100	$N_2F_2H_1$	7-19-67, LC
	L	68	--	--	--	66	20/50	$N_2F_2H_1$	7-25-67, LC
154. B. O.	R	--	F	W	43	58	LP		
	L	59	--	--	--	59	20/60	$N_2F_2H_1$	11-28-61, 5-15-62, 10-15-62, 2-11-63, 6-10-63, 8-5-64.
155. S. O.	R	68	M	W	53	69	20/20	B	8-30-67, LC
	L	--	--	--	--	68	20/20		
156. E. O.	R	65	F	W	36	66	20/30	N_1H_0	12-29-65, 9-21-66, LC.
	L	66	--	--	--	64	HM	N_1F_2	4-12-66, 1-30-67, 4-12-67, LC.

See footnotes at end of table.

C. N. JEPSON—Continued

Date of last exam	Duration of followup	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Surgery	Complications	Cause of VA loss
4–26–68	22 months	20/30	1	F_1			
4–26–68	22 months	4/300	0	F_2			Vit. hem. glaucoma.
10–31–64	51 months	20/30	1	F_1			
10–31–64	49 months	20/200	.9	F_1			Vitreous hem.
6– 4–68	12 months	20/400	0	N_1		Mac. burn	
6– 4–68		HMT					Det. ret.
5– 4–67	11 months	20/30	1	F_1			
5– 4–67	11 months	LP	.27	H_2			Vitreous hem.
9–18–67	30 months	20/25	1	$N_1F_2H_1$			
9–18–67	28 months	20/70	.8	$N_1F_2H_1$			Prog. of retin.
3– 6–68	2 days	20/40		(2)			
3– 6–68		20/40		(2)			
6–26–68	4 months	2/300	1	N_2F_2			
6–26–68	4 months	20/25	1	F_1			
11–19–67	91 months	20/20	1	B			
11–19–67	89 months	20/20	1	B			
11–19–67	27 months	20/400	1	B. mac. deg.			Mac. deg.
11–19–67	25 months	20/400	1	B. mac. deg.			Mac. deg.
3–1–68	48 months	20/40	1	F_1			
3–1–68	47 months	LP	.2	F_2			Cat.
6– 7–68	24 months	20/20	1	F_1			
6– 7–68	22 months	20/20	1	F_1			
7–22–67	5 months	20/200	0	F_0H_0			Mac. deg.
7–22–67	5 months	20/20	1	F_0H_0			
7–31–67	2 days	20/100	1	(2)			Cat.
7–31–67	1 month	LP	1	(2)			
4–18–68	46 months	20/20	1	B			
4–18–68	46 months	20/80	1	B			
6– 7–68	11 months	20/80	1	N_1F_2			
6– 7–68	11 months	20/80	.8	N_1F_2			
6–24–66		LP					Rubeosis of iris., det. ret, prog. retin.
6–24–66	55 months	LP	0	N_1F_2			
9– 1–67	2 days	20/20	1	(2)			
9– 1–67		20/20					Cat.
6–25–68	30 months	20/25	1	B			
6–25–68	26 months	HM	1	F_1			

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date and mode of therapy
157. E. O.	R	63	F	W	52	63	20/100	B	7-8-60, 8-11-60, LC.
	L	64	--	--	--	63	20/300	B	11-16-61, 10-21-66, LC.
158. C. P.	R	55	F	W	42	54	20/100	$N_2F_0H_1$	11-7-63, 7-24-64, LC.
	L	55	--	--	--	54	LP	$N_1F_0H_1$	10-30-63, LC.
159. F. P.	R	26	M	W	9	25	20/200	$N_2F_2H_1$	3-28-67, 12-14-67, LC.
	L	26	--	--	--	25	LP	$N_2F_2H_1$	4-26-67, LC.
160. R. P.	R	54	F	W	19	54	20/40	$N_2F_2H_1$	4-5-65, 6-25-65, 4-19-66, LC.
	L	55	--	--	--	51	LP	N_2F_2	1-20-66, LC.
161. L. P.	R	21	M	W	5	21	20/100	$N_2F_0H_1$	4-5-65, 6-25-65, 4-19-66, LC.
	L	--	--	--	--	20	HM, LP	--	--
162. E. D.	R	62	F	W	47	59	20/100	B	2-19-63, LC.
	L	--	--	--	--	59	20/70	--	--
163. A. P.	R	65	F	W	38	63	CF 3′	$N_2F_2H_1$	3-22-63, 5-21-63, 9-3-63, LC.
	L	65	--	--	--	61	HM 1′	$N_2F_2H_1$	3-22-63, 4-18-63, 5-21-63, LC.
164. M. P.	R	64	F	W	49	(1)	20/200	BH_1	12-14-61, LC.
	L	64	--	--	--	(1)	4/300	H_2	11-30-61, 3-1-62, LC.
165. E. P.	R	60	F	W	40	57	HM 3′	H_2	11-30-66, LC.
	L	--	--	--	--	57	HM 3′	--	--
166. L. P.	R	40	M	W	24	39	20/20	B	2-28-68, LC.
	L	40	--	--	--	40	20/20	B	3-1-68, LC.
167. R. P.	R	38	M	W	8	37	20/25	N_2H_0	2-28-68, LC.
	L	38	--	--	--	37	20/200	$N_2F_2H_1D$	3-2-68, 6-4-68, LC.
168. L. P.	R	63	F	W	47	63	20/400	F_1	8-11-64, 8-15-64, 9-24-64, 6-9-65, 6-15-65.
	L	63	--	--	--	63	HM, LP	H_2	9-24-64, LC.
169. M. P.	R	66	F	W	59	63	20/30	BF_0H_0	11-9-66, LC.
	L	66	--	--	--	63	20/30	BF_0H_0	10-11-66, LC.
170. J. P.	R	31	M	W	11	30	20/40	--	11-22-67, LC.
	L	--	--	--	--	30	NLP	--	--
171. C. P.	R	67	M	W	47	65	LP	H_2	6-15-65, 11-7-66, LC.
	L	67	--	--	--	65	CF 3′	H_2	6-18-65, 7-27-65, 10-25-65, 11-10-66.
172. G. P.	R	43	F	W	18	43	10/300	$N_2F_2H_1$	11-16-66, LC.
	L	43	--	--	--	43	20/25	N_1H_1	11-30-66, 1-4-67, LC.
173. C. R.	R	--	M	W	2	24	HM 2′	--	--
	L	25	--	--	--	24	20/20	N_1H_1	10-9-63, LC.
174. B. R.	R	62	F	W	48	58	20/200	$N_2F_2H_1$	10-4-67, LC.
	L	62	--	--	--	62	3/300	$N_2F_2H_1$	9-13-67, LC.
175. L. R.	R	69	F	W	57	69	20/40	B	10-21-65, LC.
	L	69	--	--	--	69	20/40	B	10-27-65, LC.
176. L. R.	R	62	F	W	60	60	CF 5′	$N_2F_2H_1$	2-21-63, 4-18-63, 7-22-63, 11-18-63, 7-20-64, 4-18-65.
	L	62	--	--	--	60	LP	$N_2F_2H_1$	2-21-63, 4-18-63, 7-22-63, 11-18-63.

See footnotes at end of table.

C. N. JEPSON—Continued

Date of last exam	Duration of followup	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Surgery	Complications	Cause of VA loss
2-13-68	96 months	20/50	1	B			
2-13-68	84 months	20/300	1	F_0	Glaucoma proc.		
1- 4-66	26 months	20/60	1	F_0	Cat. ext. 4-14-64.		
1- 4-66	27 months	3/300	1	F_1	Cat. ext. 2-4-64.		
4-29-68	11 months	20/200	1	$N_2F_2H_1$			
4-29-68	10 months	HM 1′	1	$N_2F_2H_1$	Det. ret. 4-18-67.		
1- 5-68	35 months	20/40	1	F_1			
1- 5-68	24 months	20/40	1	F_2	Det. ret. 1-13-66.		
5-17-66	13 months	20/100	1	F_0			
5-17-66		NLP					
3-30-64	13 months	20/70	1	B	Det. ret. 3-21-63.		
3-30-64		20/25					
7-28-64	16 months	20/60	1	$N_2F_2H_1$			
7-28-64	16 months	HM 1′	1	N_2F_2D			
3- 5-62	3 months	20/200	1	B			
3- 5-62	4 months	4/300	1	H_2			
1-17-67	2 months	LP	0	H_2		Vitreous hem.	Vitreous hem.
1-17-67		HM 3′					
4-26-68	2 months	20/20	1	B			
4-26-68	1½ months	20/20	1	B			
6-13-68	4 months	20/25	1	B			
6-13-68	3 months	HM	0	$N_2F_2H_1$	Det. ret. 6-7-68		Det. ret.
10-10-67	38 months	20/400	1	F_2			
10-10-67	37 months	HM	1	H_2			
3-29-68	16 months	20/30	1	BF_0H_0			
3-29-68	17 months	20/30	1	BF_0H_0			
12- 1-67	1 week	20/40	1	(2)			Rubeosis.
12- 1-67		NLP					
4-22-68	34 months	LP	1	H_2	Cat. ext. 9-20-66.		
4-22-68	34 months	20/400	1	N_1F_2	Cat. ext. 8-3-67.		
4-17-68	17 months	NLP	0	$N_2F_2H_1$		Det. ret.	Det. ret., prog. ret.
4-17-68	17 months	20/25	1	F_0			
3- 1-68		HM 2′					
3- 1-68	53 months	20/20	1	F_1			
4-25-68	6 months	20/200	1	F_1H_1			
4-25-68	7 months	20/50	1	F_1H_1			
5-16-67	18 months	20/40	1	B			
5-16-67	18 months	20/100	.3	B			Prog. of mac.
7-24-64	17 months	20/400	1	F_2H_1			
7-24-64	17 months	HM 1′	1	F_2H_1			

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date and mode of therapy
177. M. R.	R	31	F	W	11	29	HM	H_2	12-17-66, 4-12-66, 8-5-67, 11-27-67, 3-14-68.
	L	31	--	--	--------	29	20/200	$N_2F_2H_1$	12-14-66, 4-14-67, 8-2-67, LC.
178. V. R.	R	54	F	W	16	52	20/60	$N_2F_2H_1$	12-6-67, LC
	L	54	--	--	--------	52	3/300	$N_2F_2H_1$	11-30-67, LC
179. M. R.	R	23	M	W	13	22	CF	$N_2F_2H_1$	5-15-67, 7-8-67, LC
	L	23	--	--	--------	22	CF	$N_2F_2H_1$	5-10-67, 6-30-67, LC
180. P. R.	R	22	F	W	10	22	HM	----------	9-22-67, LC
	L	22	--	--	--------	22	20/100	----------	9-20-67, LC
181. M. R.	R	34	F	W	12	32	20/60	BH_1	3-11-66, 10-23-67, LC
	L	--	--	--	--------	32	20/40	----------	----------
182. C. R.	R	--	M	W	47	67	NLP	----------	----------
	L	67	--	--	--------	67	20/40	N_2	6-5-68, LC
183. A. R.	R	38	F	W	18	30	20/100	$N_2F_1H_1$	6-2-66, 9-6-66, 12-6-66, LC.
	L	38	--	--	--------	30	20/40	$N_2F_1H_1$	6-8-66, 9-13-66, 12-1-66 3-15-67, 4-21-67, 6-22-67, 11-28-67, 6-5-68.
184. A. R.	R	73	M	W	53	67	20/40	N_1H_0	6-21-63, 7-22-63, LC
	L	73	--	--	--------	67	20/400	$N_1F_2H_1$	6-21-63, 7-22-63, 9-16-63, LC.
185. C. R.	R	60	F	W	44	58	20/300	$N_2F_1H_1$	1-21-67, 6-21-67, LC
	L	60	--	--	--------	58	20/200	N_2	1-17-67, 6-24-67, LC
186. T. R.	R	37	M	W	32	37	20/30	B	1-27-67, LC
	L	37	--	--	--------	37	20/40	B	2-4-67, LC
187. S. R.	R	52	M	W	43	52	20/20	BN_2H_0	7-29-66, LC
	L	52	--	--	--------	51	20/400	$BN_2F_2H_1$	7-26-66, LC
188. S. S.	R	48	M	W	25	47	LP	H_2	12-16-66, 5-7-68, LC.
	L	48	--	--	--------	48	20/40	N_1H_1	12-14-66, 1-17-67, LC.
189. M. S.	R	--	M	W	33	67	LP	----------	----------
	L	68	--	--	--------	68	20/50	$N_2F_1H_1$	8-9-67, 12-26-67, LC.
190. H. S.	R	53	M	W	49	50	LP	----------	2-21-67, LC
	L	--	--	--	--------	50	HM 3′	----------	----------
191. V. S.	R	52	F	W	(1)	50	20/40	BN_2H_0	8-17-66, LC
	L	52	--	--	--------	50	20/70	BN_2H_0	8-13-66, LC
192. D. S.	R	65	F	W	50	65	20/100	$N_1F_1H_1$	3-6-68, LC
	L	--	--	--	--------	50	Anophthalmos.	----------	----------
193. D. S.	R	61	F	W	40	61	20/80	----------	6-21-68, LC
	L	61	--	--	--------	61	20/80	----------	6-17-68, LC
194. G. S.	R	54	M	W	34	52	20/400	$N_2F_2H_1$	3-22-67, 11-8-67, 5-13-68, LC
	L	54	--	--	--------	50	HM	$N_2F_2H_1$	3-29-67, 4-11-67, 7-1-67, 4-16-68
195. M. S.	R	69	F	W	56	68	3/300	$N_2F_2H_1$	2-13-63, 7-22-63, LC.
	L	69	--	--	--------	68	HMT 1′	$N_2F_2H_1$	2-13-63, LC
196. M. S.	R	--	M	W	(1)	54	LP	----------	----------
	L	55	--	--	--------	54	20/80	----------	6-17-68, LC

See footnotes at end of table.

C. N. JEPSON—Continued

Date of last exam	Duration of followup	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Surgery	Complications	Cause of VA loss
4-22-68	16 months	20/300	1	$N_1F_2H_1$			
4-22-68	16 months	20/200	1	F_1			
4-21-68	4 months	20/40	1	F_1H_1			
4-21-68	5 months	20/70	1	F_1H_1			
7-8-67	2 months	LP	0	H_2			Vit. hem.
7-8-67	2 months	20/100	1	$N_2F_2H_1$			
9-25-67	3 days	HM	1	(2)			
9-25-67	5 days	20/100	1	(2)			
4-2-68	25 months	20/50	1	B			
4-2-68		20/25					
6-14-68		NLP					
6-14-68	1 week	20/40	1	N_1			
6-14-68	24 months	20/400	.25	$N_2F_2H_0$			Prog. of retin.
6-14-68	24 months	LP	.25	$N_2F_2H_1$			Prog. of retin.
3-4-64	9 months	20/100	.4	F_1			Prog. of retin.
3-4-64	9 months	CF 2′	.4	F_2			Cat.
4-26-68	15 months	20/300	1	N_1F_1			
4-26-68	15 months	20/200	1	F_1			
5-24-68	28 months	20/20	1	B			
5-24-68	28 months	20/30	1	B			
1-24-67	6 months	20/20	1	BN_0H_0			
1-24-67	6 months	20/400	1	$BN_2F_2H_1$			
5- 8-68	17 months	LP	1	H_2			
5- 8-68	17 months	20/40	1	F_0			
1-11-68		HM					
6-30-68	10 months	20/300	0	F_2H_1			Prog. of retin.
2-25-67	5 days	LP	1	(2)	Det. ret. 2-23-67.		
		3/300	1			Det. ret.	Det. ret.
4-10-68	20 months	20/200	0	BN_2H_0			Mac. deg.
4-10 68	20 months	20/200	0	BN_2H_0			Mac. deg.
5- 2-68	2 months	20/80	1	F_1			
6-25-68	1 week	20/80	1	(2)			
6-25-68	2 weeks	20/80	1	(2)			
5-24-68	14 months	10/300	0	$N_2F_2H_1$	Pit. ablation		Prog. of retin.
5-24-68	14 months	HM	1	$N_2F_2H_1$			Prog. of retin.
4- 3-64	14 months	HM 4′	0	$N_2F_2H_1$	Det. ret. 8-27-63.		Prog. of retin.
4- 3-64	14 months	LP	0	$N_2F_2H_1$			Prog. of retin.
7-21-68		LP		(2)		Det. ret.	Det. ret.
7-21-68	1 month	20/400		(2)			

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date and mode of therapy
197. S. S.	R	65	F	W	(1)	65	20/200	B	4-7-65, 9-29-65, LC
	L	65	--	--	--------	65	20/80	B	4-24-65, 10-13-65, LC.
198. P. S.	R	50	M	W	35	48	20/40	----------	12-8-66, LC
	L	--	--	--	--------	50	20/200	----------	----------
199. C. S.	R	24	M	W	16	23	20/100	$N_2F_1H_1$	11-3-65, 12-8-65, 4-9-66, LC.
	L	24	--	--	--------	19	CF 2′	$N_1F_2H_1$	4-7-66, 10-21-66, LC
200. H. S.	R	38	M	W	13	37	LP	H_2	5-10-67, LC
	L	38	--	--	--------	38	20/25	H_2	2-23-67, 7-26-67, 8-25-67, 5-24-68.
201. S. S.	R	60	F	W	49	59	20/20	$BN_1F_0H_0$	4-30-68, LC
	L	--	--	--	--------	59	20/20	$BN_1F_0H_0$	4-30-68, LC
202. R. S.	R	--	F	W	39	60	20/200	----------	----------
	L	61	--	--	--------	61	HM 1′	$N_2F_2H_1$	4-29-68, 6-17-68, LC
203. B. S.	R	--	M	W	46	50	LP	----------	----------
	L	50	--	--	--------	50	20/70	$N_2F_2H_1$	10-8-66, LC
204. J. S.	R	42	M	W	13	42	20/60	$N_2F_2H_1$	10-5-65, LC
	L	--	--	--	--------	42	LP	----------	----------
205. M. S.	R	--	M	W	30	42	20/20	B	----------
	L	44	--	--	--------	42	20/20	B	5-8-67, 2-19-68, LC
206. R. S.	R	52	M	W	40	50	20/50	B	5-29-68, LC
	L	52	--	--	--------	50	20/60	B	5-31-68, LC
207. B. S.	R	40	F	W	18	39	LP	----------	----------
	L	40	--	--	--------	39	CF 3′	$BN_2F_2H_1$	9-6-67, 11-13-67, LC
208. H. S.	R	68	F	W	53	68	20/70	N_2F_2	12-8-67, LC
	L	68	--	--	--------	68	3/300	N_2F_2	12-5-67, LC
209. G. T.	R	40	F	W	12	34	HM 2′	$N_1F_2H_1$	5-62, 11-21-63, 12-6-63, LC.
	L	39	--	--	--------	34	20/20	B	10-6-61, 12-6-63, LC
210. A.T.	R	31	M	W	16	29	20/400	$BN_2F_2H_1$	4-27-65, 1-3-66, 3-15-66, 4-15-66.
	L	31	--	--	--------	29	20/60	$BN_2F_2H_1$	2-21-65, 10-20-65, LC.
211. M. T.	R	68	F	W	55	67	LP	$N_2F_2H_1$	3-7-68, 7-13-68, LC
	L	68	--	--	--------	67	20/80	$N_2F_2H_1$	3-9-68, LC
212. P. T.	R	--	F	W	13	29	NLP	----------	----------
	L	39	--	--	--------	35	20/80	F_2	10-23-67, LC
213. B. T.	R	36	F	W	9	26	20/40	$BN_2F_0H_1$	12-14-64, 3-10-65, 4-5-67, LC.
	L	27	--	--	--------	26	20/40	$BN_2F_0H_1$	3-22-65, LC
214. A. T.	R	61	F	W	35	56	20/70	$N_2F_2H_1$	6-9-66, LC
	L	61	--	--	--------	56	20/200	$N_2F_2H_1$	6-11-66, LC
215. M. T.	R	58	F	W	30	57	20/50	$N_2F_2H_0$	7-12-67, 10-25-67, LC.
	L	58	--	--	--------	58	20/60	$N_2F_2H_0$	6-29-67, 9-20-67, 2-13-68, LC.
216. S. T.	R	23	F	W	13	18	20/300	$N_2F_2H_1$	4-29-66, LC
	L	23	--	--	--------	18	HM	$N_2F_2H_1D$	4-29-66, LC
217. P. U.	R	21	F	W	6	21	20/30	$N_2F_2H_1$	1-28-67, LC
	L	21	--	--	--------	21	20/70	$N_2F_2H_1$	1-26-67, LC
218. J. V.	R	--	F	W	31	42	20/40	----------	----------
	L	42	--	--	--------	42	20/200	----------	11-16-66, LC

See footnotes at end of table.

C. N. JEPSON—Continued

Date of last exam	Duration of followup	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Surgery	Complications	Cause of VA loss
4-26-68	36 months	CF 1′	0	B			Prog. of retin.
4-26-68	36 months	20/80	1	BF_0			
12-13-66	5 days	20/100		(2)			
12-13-66		20/50					
10-17-67	23 months	20/25	1	F_1H_1			
10-17-67	18 months	20/60	1	F_2H_1			
5-25-68	12 months	HM	1	$N_2F_2H_1$			
5-25-68	15 months	CF 3′	0	H_2			
5- 4-68	5 days	20/20	1	(2)			Mac. deg.
5- 4-68	5 days	20/20	1	(2)			Mac. deg.
		20/200					
6-18-68	2 months	HM 1′	1	H_2		Vit. hem	Vit. hem.
10-11-66		LP					
10-11-66	3 days	HM	0	(2)		Det. ret	Det. ret.
6-23-67	20 months	LP	0	H_2			Vitreous hem.
6-23-67		LP					
6-15-68		20/20		B			
6-15-68	13 months	20/20	1	B			
6-29-68	1 month	20/50	1	B			
6-29-68	1 month	20/60	1	B			
2-12-68		NLP					
2-12-68	5 months	CF 3′	1	F_2			
2-16-68	2 months	20/70	1	H_2			
2-16-68	2 months	HM	0	H_2			
10- 1-65	41 months	20/400	1	F_1			
10- 1-65	48 months	20/20	1	B			
10-21-66	18 months	CF	.6	$BN_2F_2H_1$			Prog. of retin.
10-21-66	17 months	LP	0	$BN_2F_2H_1$			Prog. of retin.
6-30-68	3 months	CF 3′	1	$N_1F_2H_1$			
6-30-68	3 months	20/80	1	$N_1F_2H_1$			
4-27-68		NLP					
4-27-68	7 months	20/70	1	F_1			
1-15-68	49 months	20/30	1				
1-15-68	34 months	20/20	1				
5-15-68	23 months	20/60	1	$N_1F_2H_1$			
5-15-68	23 months	20/200	1	$N_1F_2H_1$			
6-17-68	12 months	20/30	1	F_1			
6-17-68	12 months	20/50	1	F_1			
5-21-68	25 months	20/300	1	F_2			
5-21-68	25 months	NLP	0	F_2	Det. ret		
7-20-67	6 months	20/40	0	F_2			Prog. of retin.
7-20-67	6 months	3/200	0	N_2F_2		Det. ret	Det. ret.
11-16-66		20/40					
11-16-66				(2)			

Number and name	Eye	Age	Sex	Race	Age at diagnosis of diabetes mellitus	Age at 1st ocular symptom	Visual acuity just prior to therapy	Classification of retinopathy just prior to therapy	Date and mode of therapy
219. J. V.	R	38	F	W	29	37	CF 4′	$N_2F_2H_1$	4-24-68, 5-29-68, LC.
	L	--	--	--		37	20/20		
220. W. W.	R	--	M	W	48	48	20/30		
	L	63	--	--		48	20/30	B	8-4-67, LC.
221. J. W.	R	21	M	W	(1)	21	10/20	B	1-6-66, LC.
	L	21	--	--		21	20/20	B	12-16-65, LC.
222. B. W.	R	--	M	W	(1)	28	20/20		
	L	28	--	--		28	20/200		11-3-67, LC.
223. L. W.	R	--	M	W	6	28	LP		
	L	29	--	--		29	20/300	$N_2F_1H_1$	2-16-66, 4-13-66, 6-17-66, 3-15-67.
224. R. W.	R	21	M	W	9	21	20/80	$N_2F_1H_1$	9-25-66, LC.
	L	21	--	--		21	20/80	$N_2F_1H_1$	10-4-66, LC.
225. G. W.	R	--	F	W	11	25	LP		
	L	29	--	--		26	20/60	$N_2F_2H_1$	6-8-66, LC.
226. J. W.	R	42	M	W	7	42	20/25	$N_2F_2H_1$	9-3-66, LC.
	L	--	--	--		42	20/40		Det. ret., 7-1-67, Surgery+LC.
277. A. W.	R	71	M	W	32	67	20/400	B	9-26-67, LC.
	L	71	--	--		67	20/60		
228. J. W.	R	45	F	W	(1)	45	20/20	B	10-25-67, LC.
	L	45	--	--		45	20/20	B	1-17-68, LC.
229. J. W.	R	45	F	W	10	44	CF 2′	$N_2F_1H_1$	6-8-63, 8-31-66, 2-1-67, 6-21-67.
	L	45	--	--		44	CF 5′	$N_2F_1H_1$	5-25-66, 9-3-66, 11-30-66, LC.
230. L. W.	R	66	F	W	46	66	20/200	$N_2F_1H_1$	5-17-62, 7-19-62, 3-23-66, LC.
	L	67	--	--		66	20/200	$N_2F_1H_1$	6-19-63, 1-2-64, 4-16-64, LC.
231. L. W.	R	43	M	W	5	43	20/20	$N_2F_1H_1$	6-22-66, LC.
	L	43	--	--		43	20/30	$N_2F_1H_1$	6-20-66, LC.
232. P. Y.	R	45	M	W	12	41	20/30	$N_1F_2H_1$	1-4-67, 7-28-67, 10-5-67, 12-13-67.
	L	45	—	—		41	20/30	$N_1F_2H_1$	1-7-67, 6-27-68, LC.
233. B. M.	R	38	F	W	28	36	20/50	$N_1F_1H_1$	7-26-67, LC.
	L	—	—	—		36			

[1] Unknown.
[2] Loss to followup.
[3] Deceased 5-20-68.

C. N. JEPSON—Continued

Date of last exam	Duration of followup	Visual acuity at last exam	Visual retention index	Classification of retinopathy at last exam	Surgery	Complications	Cause of VA loss
6- 3-68	2 months	HM	0	$N_2F_2H_1$			Det. ret.
6- 3-68		20/20					
8- 4-67		20/30					
8- 4-67				(2)			
6-26-68	29 months	20/20	1	B			
6-26-68	30 months	20/20	1	B			
11- 3-67		20/20					
11- 3-67				(2)			
3- 4-68		LP					
3- 4-68	25 months	20/200	1	F_1			
12-12-66	3 months	20/70	1	F_2			
12-12-66	2 months	NLP	0	N_2F_2			Glaucoma.
6-28-67		CF 5′					
6-28-67	12 months	20/40	1	N_1F_2			
9-22-67	12 months	20/25	1	F_1			
9-22-67		20/400			Det. Ret., 9-7-66.		Mac. pucker.
5-29-68	8 months	20/60	1	B	Cat. ext. 1-16-68.		
5-29-68	8 months	20/80					
6-27-68	8 months	20/20	1	B			
6-27-68	5 months	20/20	1	B			
1-31-68	19 months	20/400	1	F_2			
1-31-68	19 months	20/30	1	F_2			
5-23-67	60 months	20/80	1	F_1			
5-23-67	60 months	20/80	1	F_1			
10- 5-66	4 months	20/20	1	N_1F_2			
10- 5-66	4 months	20/25	1	N_1F_2			
6-30-68	19 months	20/100	.5	F_2			Prolif. in mac.
6-30-68	19 months	20/25	1	F_2			
6-30-68	11 months	20/30	1	F_1			
6-30-68							

Index

Index

A

Aarhus Kommunehospital, Aarhus, Denmark, 291, 293
Ablation
see Pituitary ablation
Abnormalities, venous, XXII, 12
microvascular, 9
questionable, 21
Acid-Schiff staining method, 61
Ackerman, Irving R., 275
Acki, T., 688
Acromegaly, 274, 402
diabetic acromegalics and retinopathy, 408
Marie's 1886 description of, 148
radiation, and, 149
retinopathy and 75 acromegalics, 401
Acta ophthalmologica, 680
ACTH
see Hormones
Acuity, visual
see Visual acuity
Adams, Donald A., IX, XIII, 341–354
Adams, J. H., 195, 202, 247
Adenohypophysis, destruction of, 368
ADH
see Hormones
Adhesions, vitroretinal
see Vitroretinal adhesions
Adjustment of patient before pituitary ablation, 177
Adler Foundation, Inc., 153, 437
Adrenal cortex investigation, 242
Adrenal crisis, 271, 272
Adrenal function
endogenous, 716
evaluation, 203
pituitary ablation, following, 179
tests of, 334
Adrenal insufficiency, 188, 201
Adrenal steroids
see Hormones
Adrenalectomy, 393, 564
Adrenocortical insufficiency, 209
Age and blindness risk, 44
Age and visual prognosis, 41
Age distribution variations in patients undergoing photocoagulation and cryohypophysectomy, 541
Age of diabetic patient
diabetic retinopathy development, chances of, and, 109
progression and regression of diabetic retinopathy, chances of, and, 110
Aiello, Lloyd M., VIII, X, XII, XV, 153–169, 437–653, 609, 610, 613, 615, 619, 620, 624, 627, 638, 639, 640, 641, 654, 665–671, 714, 718
Airlie House Symposium, 267
personal impressions of Davis, the, 718–719
Airlie House classification of diabetic retinopathy, XX, 23, 30, 35
Alcian blue staining, 673
Algvere, P., 683, 689
Alvis, D. L., 169
Amalric, P., 168, 169, 506, 592
Amenorrhea, 220, 221
pituitary ablation, following, 204
American Cancer Society, Inc., 332
American Journal of Ophthalmology, the, 569
American Optics ruby laser, 637
Amethocaine, 480
Amnesia without pain, 427–428
Ampicillin, 239
Amputations, vascular disease leading to, 233
Anabolic steroids, 119
of no value, 119
Analysis of data by computer, 20
Analysis of photographic material, 65–66
Anatomic and visual results of photocoagulation
discussion of, 612–622
summarized, 607–611
Anatomical anomalies of pituitary, 239

Anatomical studies of the sella turcica
described, 365–370
illustrated, 367
Anatomical variations in pituitary and carotids, 430
Andersen, Hans C., IX, 291–311
Androgens
see Hormones
Anemia, 188
following pituitary ablation, 179
surgery, after, 397
Anesthesia
Amethocaine in, 480
cryohypophysectomy, in, 344, 538
diabetic, and the, 196
photocoagulation, in, 556, 566, 781
pituitary ablation, and, 201
retrobulbar, not required in ruby laser photocoagulation 619, 623
surgical pituitary ablation, in, 198
Aneurysms
aneurysm formation and lipid metabolism relationship?, 116
formation of, 66
fusiform, 9, 13
not clinically apparent, will fluorescein show them?, 653
Angina pectoris, 177, 229, 426
Angiography
see also Fluorescein
carotid artery location demonstration, for, 428
fluorescein fundus type, 9
fluorescein study of, the, 167
fluorescence type, 596
Angiopathy, 253
See also Diabetic retinopathy
angiopathic retinopathy
documentation of in criteria, 313
male more susceptible than female, 222
radiofrequency pitutiary coagulation in, 210
angiopathy-proliferation correlation, degree of, 258, 259
angiopathy ratio, 254
arrest no guarantee of immunity to further hemorrhages, 273
average ratios in 87 eyes, charted, 257
Angiopathy—Continued
diffuse, 167, 444, 453, 454
fluorescein photography showing, 157
heart, in the, 351
leakage, with, 455
severe, illustrated, 458
hemorrhage, and, 186
decreased after ablation, 187
hypophysectomy for, 291–311
kidney, in the, 351
preoperative grades, 255
preoperative, vision outcome and, 258
progressive
manifestation of, 314
stalk section for, 313
proton beam treatment and, 256
slowest possible progress of, 143
tabulated, 254
Animal experiments, 115, 195
inferences drawn from, 143
radioactivity-tagged blood absorption in, 552
ruby laser's effect on monkey retina, 665–671
Anosmia, 361
Anoxia a neovascularization trigger mechanism? 56
Anterior pituitary ablation, selective, 235–247
Anticonvulsants, 230
Antidiuretic hormone syndrome following cryohypophysectomy, 345
Antiglycosemic agents, response of, 267
Apparatus, different type of classifications, and, 36
Appelmans, E., 46
Appels, A., 729
Aphasia, postictal, 361
Apituitarism, 403
Arachnoid, tearing of the, procedure following, 430
Arginine, 281, 282
infusion, 716
infusion tests, 281, 282
test results charted, 284
Argon laser, the, 481
Arterial abnormalities, 380
Arterial insufficiency and retinopathy, 49

Arterial strands, preservation in stalk section, 359
Arterial tension, retinal, 659
Arteries, photocoagulation of, 524
Arteriograms, carotid, reliability of questioned, 368
Arteriolar abnormalities, 17
no standard photograph for, 17
Arteriolar and capillary closure, 49
Arteriolar hypertension, 660
Arteriolar hypotension, 660
Arteriolar involvement, opthalmoscopic evidence of, 50
Arteriolar lesions, glomerular, 222
Arterioles
abnormal, illustrated, 68, 69, 70
occluded, illustrated, 71
pathological, 57, 58, 61–63
terminal, hyaline, construction of, 50
Arteriosclerosis, 426
evaluation for hypophyseal stalk section, and, 223
retinal disease and neovascularization of arteriosclerotic retina, 450.
ruby laser photocoagulation and, 450
ruby laser photocoagulation, and, 461
subjects with P.D.R., examination findings in, arteriosclerotic, 63
Arteriovenous communications formation, 71
Arteriovenous shunts
capillary closure preceding, 93
formation illustrated, 77
Artery, ophthalmic—carotid, a direct branch of, 657
Ashton, N., 53, 61, 64, 79, 466, 476
Assessment of pituitary ablation, 242–246
Assessment, serial, 6
Asymmetry
asymmetrical diabetic retinopathy tabulated, 660
extreme degree occurring in retinal occlusion, 660
Atherosclerotic disease, 172
Atomic nuclei used in pituitary ablation, 416
Atrophy, optic, 17, 473 530, 652
central retinal artery embarrassment secondary to, 601
illustrated, 533
photocoagulation and, 720
photocoagulation, ascribed to, 611
Attenuation of normal vessels of retinal system, 56, 61
Audience poll regarding course of treatment, or no treatment, in retinopathy, 652
Autoradiographic studies, 673–680
Avascularity, fluorescein photography, and, 157
Awaya, S., 688
Azotemia, 210, 333, 337, 425
azotemic patients could receive radiofrequency pituitary coagulation?, 210
postoperative, 177

B

Babel, J., 60, 64
Bacitracin solution in pituitary ablation surgery, 200
Background diabetes, 100
Background retinopathy, XXI, 41, 97, 109, 570, 571, 720
diminution following hypophysectomy, 308
illustrated, 578
photocoagulation in, 612
treatment for, 41
Bailey and Davidoff's histological finding in acromegaly, 148
Baladimos, Marios C., X, XV, 135, 153–169, 191, 377, 380, 383, 431, 437–463, 646
Barker, S. B. 310
Barrier, mechanical, necessary in stalk section, 341
Basal metabolism test, 174
Baum, 636
Becker, Bernard, X, XV, 79, 102, 380, 283, 286, 387, 338, 389, 390, 391, 392, 477, 660, 663
Beetham, William P., VII, VIII, X, XV, 23, 30, 31, 34, 35, 37, 46, 60, 64, 90, 91, 94, 95, 99–103, 100, 101, 174, 191, 194, 195, 202, 209, 212, 225, 276, 339, 428, 430, 437–463, 475, 477, 494, 568, 609, 610, 611, 609, 622, 638, 641, 644, 646, 709, 724, 729

Beetham's statistics, confusion over, 99
Behavior assessment in patient evaluation for cryohypophysectomy, 343
Behrendt, Thomas, IX, XII, XIII, 169, 203–212, 216, 220, 225, 657–663, 724, 729, (Data) 739–742
Benefit of treatments suggested but not proved, 710
Bergland, R. M., 202
Berkeley group, the, 416, 417, 725, 727
Berkow, Joseph W., VII, 87–91, 98, 225, 228, 477, 568
Bian, C., 169
Biasotti, A., 310
Billroth's quotation, 147
Binocular indirect ophthalmoscope, 470
Bioflavinoids, 81
Biomicroscopy, slit lamp, 47
Biopsies, renal before pituitary ablation, 177
Birmingham (England) blindness survey, 43, 46
Bjorkesten, G., 728
Blach, Rolf K., IX, XV
Bleeding
  anesthesia for photocoagulation, following, 599
  photocoagulation, and, 472
Bleeding point, the approach to, 632
Blind diabetics
  guide dogs, and, 97
  rarely return to Seeing Eye Inc. for second guide dog, 87
  retrospective study on, 87
Blindness
  British-American statistics comparison, 45
  causes distribution, 262
  causes of, leading, V
  diabetes a leading cause of new, 465
  diabetes easier to control in, 557
  diabetic
    epidemiology of, 43–45
    retinopathy a leading cause of new, 537–544
    retinopathy, causing, V, 437, 485
    U.S. incidence, 465
  discovery of diabetes and onset of, interval of, tabulated, 88
Blindness—Continued
  duration prior to death in 85 diabetics, 87
  economic, defined, 42
  endocrine-sensitive lesions, and, 269
  epidemiological studies, 45
  hemorrhage, and, 266
  hemorrhage causing, 417
  hypophyseal stalk section patients, in, 213, 214
  incidence, 43–45
  legal, 87, 253, 262
  legal, definition of, 30, 42
    preoperative presence of, 260
  onset of blindness to death interval tabulated, 89
  "non-occurring in one year, unlikely to do so in next few years," 97
  photocoagulation cannot prevent in some patients, 610–611
  pituitary ablation, following 193
  price for prevention of, 193
  produced by disease having abnormality in retina and iris, 388
  proliferative retinopathy time factor in, 43
  risk of and age of patient, 44
  severe definition, 87
    poor prognosis for life in, 91
  statistics, British, 43–45
  threatened, pituitary suppression in, 249
  total, 253
    causes of, 53 eyes, in, 265
  unilateral, 215
  visual impairment and, age and, 41
  vitreous hemorrhage, and, 97
Blood flow and hypophysectomy, 380
Blood density in vitreous gel graded, 511
Blood glucose determination, postoperative, 206
Blood in the vitreous, 385, 511–512, 559–560
Blood pressure
  hypophysectomy, following, 300
  readings and hemorrhages, 126
  yttrium-90 implant, following, 320
Blood sugar
  clinic sugars and "unsuspecting" sugars, differences between, 134
  determination of, 120

Blood sugar—Continued
findings and diabetic retinopathy, 135
findings in English study, 135
low—less damage to vessels, correlated with, 140
sampling differences, 134
vascular disease, and——is there a relationship?, 144
wide mean of, a, 107
Blood urea
blood pressure, and—age of onset of diabetes, and, 125
type of urea and retinopathy, 126
Blood vessel size decrease after photocoagulation, 640
Bloodworth, J. M. B., Jr., 116, 118, 466, 476
Boden, G., 191
Body weight determination for postoperative fluid and electrolyte management, 205
Born, J. L., IX, 277–289
Bousnes, R. W., 310
Bradbury, S., 311
Bradley, Robert F., VI, VIII, X, XII, XIV, 137, 139, 140, 153–169, 171–191, 202, 247, 275, 276, 392, 393, 395–399, 401, 404, 407, 410, 425, 432, 433, 437–463, 653, 707, 713–717
Bragg peak of proton beam
centered on sella turcica, 251
hypophysectomy, 249–276
data on, 751–761
method endorsed, 273
pituitary suppression, used for, 249–276
types of irradiation, speed of effect of, 425
Breast enlargement, 208
British series—difficulty of comparison with U.S. series, 412
Brockhurst, R. J., 506, 543
Bruch's membrane, 666, 667, 668
illustrated, 676
Bruntse, Else, IX, 291–311
Buckling procedures, 630, 631, 632, 634
see also Scleral buckling
Burday, S. Z., 289
Burditt, A. G. F., 79, 83, 113, 115, 117, 126, 288, 477
Burn of the macula, photocoagulation, by, 599, 618

C

Caird, Francis J., VII, VIII, XV, 32, 37, 41–46, 79, 85, 97–113, 100, 113, 117, 128, 129, 130, 133, 136, 138, 140, 141, 142, 143, 234, 288, 339, 474, 477, 567, 609, 613, 621, 714, 715, 718
Caird—three points summarized, 130
Caird's statistics—confusion over, 99
Campbell, C. J., 442, 462, 638, 646, (Data) 820–827
Cancer of the breast, hypophysectomy in, 236
Capillaries
aneurysmal dilatation of, 157
dilated, 9
interpretation of, 167
capillary closure, 385
anatomical variation, and, 159
arteriovenous shunts, preceding, 93
cotton-wool spots and, 69–72
fluorescein photography, and, 157
illustrated, 71, 77
important early change in diabetic retinopathy, 93
capillary abnormalities and neovascularization abnormalities distinctions, 4
capillary dilatations and photocoagulation, 577
capillary network, preretinal, 528
capillary obliteration, 48
capillary occlusion, 101
capillaries rarely open, 103
capillary shunts, abnormal, illustrated, 597
Carbocaine, 470
Carbohydrate mechanism—diabetes mellitus a metabolic defect of, 227
Cardiac decompensation, 229
Cardiac disease, 253
Cardiac failure, borderline, 177
Cardiac impairment a contraindication for pituitary ablation, 231
Cardiomegaly, 177
Cardiovascular collapse, 359
Cardiovascular function, pituitary ablation patients, in, 229

Cardiovascular status, evaluation techniques, 426
Carlson, R. A., IX, 277–289
Carotid occlusive disease, 473
Cartilagenous graft in microsurgery for pituitary ablation, 239
Case Western Reserve University School of Medicine, 332, 419
Cataracts, V, 17, 30, 85, 88, 253, 262, 264, 469, 513, 599, 636
  grossly impaired vision, causing, 88
  retinopathy following removal, 651
Caulfield, J. P., 225
Central retinal artery conclusion, 315
Centrifugal nerves hypothesis, 410, 411
Cerebrospinal fluid
  hazard in transsphenoidal approach, a, 434
  leak, 423
    prevention following hypophysectomy, 239
  protects from cold?, 428
  rhinorrhea, 194, 210
    see also Rhinorrhea
  withdrawal during stalk section, 355, 356
Cerebrovascular accidents, 217, 272, 445
Chabanier, H., 291, 310
Chaney, A. L., 310
Changes, choroido-retinal, late, 60–61
Chazan, Bernard I., X, 437–653
Chloramphenicol, 205
Chlorpropamide, 347
Cholesterol, serum, 229
Chong, C. Y., IX, 277–289, 715
Chorioretinal adhesions,
  formation of, 608
  photocoagulation causing, 473, 720
Chorioretinal degeneration, 530
Chorioretinal lesions, disseminated, 453
Chorioretinal scarring, 473
Chorioretinitis, 453, 638
  disseminated, 438
Choroid, normal, illustrated, 675
Choroidal vessels, diabetic, illustrated, 679
Choroiditis, disseminated 582
Choroido-retinal changes, late, 57, 58, 60–61
Cibis, P. A., 22, 477, 482, 484, 487, 488, 494, 506, 535, 542, 543, 553, 568, 601
Cicatricial tissue formation, 56
Ciliary processes illustrated, 674, 677
Cinephotography, 216
Circulation, retina, of the, 662
Circulation time retina, in the, 662
Ciric, I. S., 202, 247, 276, 332, 339, 353
Classification
  diabetic retinopathy, of
    see Airlie Classification
    see O'Hare Classification
    see Hammersmith grading system
  apparatus differences, and, 36
  common language required, 8
  communication, and 22
  deterioration, and speed of, 36
  different functions for, 25
  discussion of, 23–37
  double blind study, 27
  fluorescein category, and the, 29
  fluorescein studies, of, 35
  functional category, a, 32
  Gallup Poll analogy, 25
  generally accepted classification necessary, 94
  hemorrhage, in, 23
  immediate determination of, 26
  importance of an excellent type of, 37
  "keep it simple," 33
  Lee, of, 507
  meaningful data with more photographs, 24
  minimal examinations in, 34
  "minimal skeleton," a, 29
  monochromatic green light in, 29
  montage, photographic, and, 24
  more sensitive type needed, 24
  morphologic, a, 32
  nine fields should be photographed, 25
  observation technique, based on, 36
  "1.5" category?, 24
  patient classification query, 94
  patients for laser photocoagulation, of, 603
  photographs, based on, 9
  preliminary, 36
  prognosis, and, 32
  proliferative lesions, of, 14

Classification—Continued
rapid progression of retinopathy, and the, 37
Republicans-Democrats analogy, 24
required—a standard relevant to ophthalmology, neurosurgery, and internal medicine, 28
requirements of a suitable type, 8
retinopathy components essential, of, 713
scheme devised for Symposium, XXI
semantics of "background", 29
simple type—proliferative and nonproliferative, 23
simplicity, and, 24
skeleton type, 24
speed of, O'Hare and Hammersmith systems compared, 29
validation of methods, 27–28
validation of photographs in, 33
Van Heuven, of, 507
venous dilatation of, 13
venous irregularities, and, 33–34
visual acuity, functional, and, 31
worst field should not be reference field? 24–25
Claudication, intermittent, 292
Cleasby, Gilbert W., X, XV, 465–477, 623, 624, 627, 719
Clinical impressions following ruby laser photocoagulation, 452
Clinical medicine and communication, 7
Closs, K., 310
Coagulation
see also Photocoagulation *and* Pituitary ablation
see also Radiofrequency pituitary coagulation
radiofrequency pituitary coagulation for angiopathic diabetic retinopathy, 203–212
Coats' disease, 472
Cochran, W. G., 562
Cogan, D. G., 53, 169, 466, 476, 671
Collins, W. F., Jr., IX, XIII, XX, 331–339
Color vision—Ishihara test tables, 682
Columbia-Presbyterian Medical Center, College of Physicians and Surgeons, New York, 545
Columbia University, ultrasound laboratory at, 635
Colwell, J. A., 567
Coly-Mycin, 239
Coma and insulin deficit, 138
Comberg's xenon arc photocagulator, 552
Communication and classification, 22
Communication between diabetic retinopathy investigators, V
Communication between study centers, 4
Communication language problem in clinical medicine, 7
Complications, ocular, 17
photocoagulation, following, 599–600
photocoagulation of, 610, 611 listed, 518, 629
Computerization of data at suggested depository, 20
Connective tissue growth, proliferative lesions, in, 16
Connell, A. M. S., 247
Connelly, C., 247
Constam, G. R., 113, 115, 117, 128, 133
Contact lens, precorneal, classification, in, 36
Contractile vasomotor function, 48
Contraction, vitreous, 93
photocoagulation, following, 490
remission, and, 485
Contreras, Joel, 149–150, 354, 723, 729
Control of diabetes
see Diabetes, control of
Control groups in pituitary ablation studies, 388
Control of diabetes, 714, 715
Control, metabolic
see Metabolic control
Controls needed in photocoagulation therapy research, 621, 622
Convulsive episodes following pituitary ablation surgery, 200
Copenhagen series
see also Photocoagulation
Copenhagen photocoagulation series grouping details, 495–499
Cordis injector, 441
Corn oil diet in retinopathy, 644
Corneal opacification, 599–600
Coronal sinus, its importance in pituitary ablation surgery, 197

333-611 O - 69 - 57

Coronary artery disease, 346
Coronary disease, hypophysectomy and, 332, 333
Coronary insufficiency, 292
Corticoids, urinary, assessment of, 242
Corticosteroid and atropine ointments, 471
Corticosteroid reserve fortified preoperatively, 205
Cortisol administration, 334
Cortisone, 180, 285, 405
Cortisone acetate administration, 178–179
  preoperative, 230
Cortisone therapy, 335
Coscas, G., 169, 506
Counting devices and image intensification, 33
Cotton-wool exudates, 13
  do they represent infarcts?, 100, 101
Cotton-wool spot area and arteriole feeding it, illustrated, 74
Cotton-wool spots, 65
  absence and disappearance of, 75
  capillary closure, and 69–72, 75
  change in total area of, illustrated, 73
  diabetics, in, 76
  disappearance of, illustrated, 75
  fluorescein picture of, 76
  hypertensive patients, in, 76
  illustrated, 67, 68, 69, 70
  patients over 40 and under 40, in, 73
  survival time of, 70
  young diabetic patient, in, illustrated, 72
Coxe, William, XV
Cranial approach to pituitary ablation, 195
Cranial nerve damage absent following coagulation-type pituitary ablation, 206
Craniotomy
  dilantin therapy following, 335
  morbidity absent in series, 335
  refused—pituitary suppression, and. 253
  relatively safe, 196
  stalk section, 395
Craniotomy—Continued
  stalk section, and pituitary suppression by proton beam an alternative procedure, 249
  stalk section, and stress of, 249
  stress, surgical, and its, 249
  transfrontal, 331
    pituitary ablation, in 229
  unsuitable candidates for, 333
Creatinine clearance, endogenous, 231
Criteria
  patient selection, for, 417–418, 507, 508
    pituitary ablation, for, 175–178, 250, 292, 423
    summarized, 375–377
Criteria used for patient selection at Johns Hopkins Hospital, 564–565
Cryohypophysectomy, 341–354, 692, 768–772
  anesthesia in, 344
  data on, 768–772
  discussion on, 351–353
  effective, simple and safe technique of pituitary ablation, an, 351
  endocrine replacements following tabulated, 347
  endocrine responses and management following, 347–348
  endocrine tests prior to, 343
  evaluation of patients for, 342–346. 538
  fundus photography in, 348, 349, 350
  hand signals taught to patient for use in surgery, 344
  hypoadrenal crises infrequent following, 347
  light coagulation as an adjunct to. 537–544
  methods and materials for, 342–346
  mortality absent in 31-patient series, 346
  ocular responses, 348–350
  operative procedure, 344
  part and whole destruction of pituitary by, 428
  patient followup in 31-patient series, 346
  patient selection—ocular standards for, 352
  patient suitability discussions at UCLA School of Medicine, 343

Cryohypophysectomy—Continued
photocoagulation, and, 648
preparation for, 344
procedure, neurological, 343
psychiatric evaluation of patients for, 343
results in 31-patient series, 346–350
retention of vision following, 348
roentgenograms taken during, 345
surgical complications, 344–346
31-patient series, in a, 342
transsphenoidal, 395
Cryoprobe, the, 343, 344
Cryosurgical probes in pituitary ablation, 194–195
Cryotherapy—retinal detachment, for, 635
Cushing, Harvey—experiments of, the, 148
Cushing's disease, 274
Cyclotron, Harvard—pituitary suppression, used in, 250
Cyclotron Laboratory, Harvard University, Cambridge, Mass., 691
"Cyst" and retinal elevation, 16

D

Daels, H., 46
Das, Tulsi, 477
Dangerfield, 641
Daniel, P. M., 195, 202
Dashe, Alfred M., IX, XII, 191, 341–354
Data
analysis at suggested depository, 20
available—treatment comparisons based on, XX
disparities, explanation in University of Wisconsin study, 83
patients'
digital system used in recording, 256
IBM sorter and punch cards used for, 256
summary, 780–781
David, N. J., 169
Davidoff, Frank, XV, 411
Davis, Matthew D., VI, VII, VIII, XII, XIV, XIX, XXI, 7, 22, 23, 24, 25, 30, 31, 32, 35, 37, 47–53, 58, 59, 79, 81–85, 93–95, 100, 101, 102, 127, 128, 132, 386, 475, 476, 494, 514, 553, 562, 567, 617, 621, 636, 650, 652, 653, 701–710
Symposium, personal impressions of, 718–719
Death
causes of, 271, 717
unrelated to pituitary ablation and diabetic retinopathy, 337
incidence of, 717
pituitary ablation, following, 230
transsphenoidal hypophysectomy, after, 295
Deckert, T., 46, 90, 91, 100, 288, 474, 477, 568, 689
Depository for collection of data, 20
functions of, suggested, 20
Detachment, macular, 85
Detachment, retinal, 57
see also Retinal detachment
proliferations, and, 16
traction, and, 468
Detachment, vitreous, 35, 51
prognosis and, 35
Deterioration, visual, tabulated, 42
DeRezende, J., 592
DeRouck, A., 688
DeSa, S., 592
deVenecia, Guillermo, VII, 47–53
Dexamethasone, 201
cerebral edema, to minimize, 79
Diabetes
age and sex of patients, 111
age of onset and diabetic control, tabulated, 123
age of onset and duration of disease relationship, tabulated, 508
blindness, the second leading cause of, V
blood glucose determination and, 147
"brittle", 445
control of, 97–113, 119–128
assessment of, 120
assessment of eyes, and, 121
categories of, 121, 127
data on, 731–38
difficulty in estimating, 116
first five years of patients' diabetic life, in, 141
Hammersmith study, 119–128
hemorrhages and microaneurysms, and, 126

Diabetes—Continued
control of—continued
irregular absorption of food, and, 133
"matters less as you go along," 139
measures difficult to establish, 129
methods of, 142
new vessels, and, 125
patient factors in, 127
results of Hammersmith tests, 122
retinitis proliferans, and, 125
retinopathy frequency, and, tabulated, 137
sugar level, and, 139
terminology, controversy about, 135
vascular disease, and, 115, 129
visual prognosis, and, 41
correlation between frequency of retinopathy after diagnosis of, III
current knowledge of fragmentary, 555
details of in patients receiving hypophyseal stalk section, 214
Diabetes and Arthritis Control Program, XX
Diabetes Foundation, Inc., Boston, Massachusetts, 153, 171, 437, 665
diabetes insipidus, 188, 207, 210, 273, 405
correction of, the, 230
cryophypophysectomy, following, 345, 346
pitressin, needing, 421
postoperative, 206
treatment for, 335
unknown after yttrium-90 implantation, 423
diabetes mellitus, 246
carbohydrate mechanism, a metabolic defect of, 227
causation obscure, 222
control and the progression of retinopathy, 115–118
factors involved in, 465
incidence, 465
insulin in the control of, 227
longevity, and, 465
pathogenesis, 465–466
pathologic vascular alteration of unknown mechanism, 465
pathophysiology, 466
Diabetes—Continued
diabetes mellitus—continued
renal function affected by, 227
"there is no cure for," 593
vascular complications of, 465
vascular tissue, affecting, 227
diabetic and fertility, the, 193
diabetic angiopathy
early clinical appearance, 292
spontaneous course of, changes after hypophysectomy, and, 291
diabetic conditions tabulated in 30 cases, 240
diabetic ketoacidosis, 140
diabetic patients, compulsive, 138
diabetic proliferating retinopathy—ruby laser photocoagulation for, 437–463
diabetics, juvenile, treatment of, 143
diabetics, longer life expectancy of, V
diabetogenic factor, removal of, 245
diabetologists, 277
diabetologists and the Hammersmith grading technique, 3–4
diagrammatic plotting of microaneurysms, 65
see also Fundus diagrams
discovery of disease–onset of blindness interval, tabulated, 88
disease affecting metabolism of retinal tissue, a, 29
does uncontrolled diabetes hasten retinopathy? 117
duration at time of Hammersmith study, tabulated, 122
duration when retinopathy diagnosed, tabulated, 122
easier to control when patients become blind, 557
frequency of retinopathy, and, 111
genetic, 116
growth-onset type, 42
dominant trait, a, 193
hypophysectomy, and, V
maturity onset type, 42
mean age at diagnosis in two types of retinopathy, 126
medical management of, improved, V
"mild diabetes," 135
mild maturity-onset type, retinopathy, and, 135

Diabetes—Continued
onset-of, data needed on, 23
pancreatic, 116
patient motivation must be developed, 117
reduction of complications in, 110
treatment, approach to, 115
treatment in different control groups, 123
unstable, 446
Diabetic retinopathy
adult onset type, 81
advanced type—prognosis for retaining vision in second eye poor, 91
advanced type—visual prognosis in, 87–91
Airlie classification of, XX, 7–37
angiopathy, grade of before treatment, 699
"arrested" following medical treatment, 171
arterioles in, normality of, 50
asymmetry, retinal occulsion and, 660
background type, 570, 571
background type cases compared with proliferative cases, 572
"better control" of, 714
blindness, causing, statistics on, 45
blindness, new, a leading cause of, V, 537–544
cardiac complications and life expectancy, 278
categories in O'Hare classification of, XXII
cause unknown, 115
classification, addendum to, 22
classification of, XIX, XX
lack of, a, XXI
of components essential, 713
tabulated, 254
clinical course of viewed as increasing ischemia, 47, 48
comparisons of treatment methods, 691–700
control of diabetes mellitus, and the, 115–118
corn oil diet in, 644
cryophypophysectomy, and, 341–354
data on 30-patient series, 240–241
Diabetic retinopathy—Continued
degree of ablation and response to treatment, correlated, 324
development in patients with serial observations and initially normal fundi, 108, 109
development stage and randomization between operated and not operated, tabulated, 293
diabetes control and frequency of conclusions, 112
diabetes, control of, and, 97–113, 119–128
diet in, 563
dreaded vascular complication, a, V
early controversy on, 148
early hypophysectomy for, 149
early manifestations of, 653
early nonproliferative phase, 8
early progressive type, 508
early stage therapy, 632
economic difficulties of patient, 555
effect of diabetic control on, 119–128
effect of photocoagulation therapy, 471–473
ERG in, 681–689
evaluation of, need for uniformity in, 7
examination before treatment, 409
features of, defined, 3
fluorescein diffusion correlated with severity of, 159
fluorescein photography before and after pituitary ablation, 153–169
frequency in relation to duration of diabetes, 109
fundamentally proliferative, is, 52
genetic variables, and, 116
granular blood flow in, 49
growth hormone secretion, and, 287
hemorrhagic—pituitary ablation in, 171
hormonal pituitary mechanism involved in, 235
hormonal suppression in, 563
hormonal variables, and, 116
"how much reduction of pituitary function is required for palliation of?"
hypophyseal stalk section for, 213–225, 313–316

Diabetic retinopathy—Continued
hypophysectomy for, 193–202, 291–311, 336, 563
hypothesis of the neural mechanism in pathogenesis of, 235
initial events in the course of, 48
intercurrent illnesses, and, 136
investigators of, communications between, V
"is total hypophysectomy necessary?", 351
juvenile onset type, 81
laser photocoagulation treatment for, 603–605
mean age at diagnosis of diabetes, 726
medical aspects of pituitary ablation, discussion of, 400–413
metabolic alterations, and, 351
metabolic control and, prospective study, 132
metabolic control relationship, XIX, 132–144
method of grading the course of, 131
natural course of, long-term study of, 47
natural course of 321 eyes followed one year or more, 81–85
natural history of, XIX, 65–79, 614
conclusions and summary, 78
summary of papers on, 78, 93–95
unpredictable, 3, 72
neural mechanism in pathogenesis of, 235
new vessels in, XXI, XXII
nonproliferative cases tabulated, 608
observations on hypophysectomy for, 193–202
ocular aspects of pituitary ablation for, discussion of, 380–393
O'Hare classification
see O'Hare classification
older patients have worse prognosis, 133
171 eyes with, followed one year or more, tabulated summary, 84
onset of, age of, prognosis, and, 285
ophthalmoscopic appearance of, 437
ophthalmoscopic beginnings of, 48
ophthalmoscopic classification of, 16–17
overall disease, interest in, 32
Diabetic retinopathy—Continued
overall response to yttrium-90 implant treatment tabulations, 327
palliation of, "how much pituitary function reduction is required for?", 278
pathogenesis of, 662
clinical observations on, 47–53
definition required, 151
pathogenetic sequence of, 547
pathophysiological investigation, a, 235–247
patient evaluation in, V
patients with less seem to have better control of diabetes, 115
paucity of statistical studies on, 474
photocoagulation in, V, 437–653, 465–477, 507–514, 563, 720–721
see also Photocoagulation
Mortimer's 64-patient series, 515–521
results of, 569–592
results in 127-patient study, 577–578
results, discussion of, 612–622
reviewed in 232-patient study, 593–601
summary of papers on treatment techniques, 623–629
photocoagulation treatment.
discussion on, 630–653
rationale, 607–608
photographic standards in classification of, 7
pituitary ablation in, V, XIX, 227–234, 331–339
see also Pituitary ablation
and photocoagulation comparisons, 709
beneficial, 150
discussion of ocular aspects of, 380–393
historical summary, an, 147–151
methods summarized, 341, 342
pituitary functions responsible for, 411
pituitary stalk section less reliable than total hypophysectomy, 171
pituitary suppression by heavy particle therapy
see Pituitary suppression

Diabetic retinopathy—Continued
practical experience with a method for grading, 3–6
pre-proliferative and proliferative phases blend imperceptibly, 51
pressure measurements in diabetic eyes, 660
prevention and management of, 117
prognosis, ERG an aid in, 688
progression, great variation in, 713
progressive proliferation, 513
proliferative
see Proliferative diabetic retinopathy
puberty, demonstrated prior to, 683
radiofrequency pituitary coagulation for, 203–212, 365–373
rationale for photocoagulation for, 545–553
recognition of a relatively recent event, 147
regression of, 60–61
relative ineffectiveness of therapeutic means, 485
remissions, spontaneous, characterized by, V
renal complications and life expectancy, 278
resolution of disease in high percentage of cases undergoing pituitary ablation, 338
response to yttrium-90 implant treatment, analyzed in terms of age and blood pressure, 325
retinitis proliferans—photocoagulation for, 555–562
review of selected aspects of, 713–717
role of photocoagulation in, 485–494
severe juvenile type, 582
severity correlated with visual deterioration, 90
severity of related to visual acuity, 508
simple—ERG readings, in, 684
spontaneous pituitary infarction, and a, 341
spontaneous regression of, 622
spontaneous remission of, 518
spontaneous reversibility of, possible, 175
stabilization following surgical pituitary ablation, 171
stalk section in, 355–364
see also Stalk section
statistical report on, 53
stress, and, 116
study centers, communication between, 4
surgical aspects of pituitary ablation
discussion of, 422–434
summary of, 415–421
surgical pituitary ablation in, 171–191
survival statistics—pituitary suppression, after, 279–281
symptoms are reversible, early, 592
therapy for, V, XIX
30 cases, data on, 240–241
321 eyes with, followed one year or more, tabulated summary, 84
treatment for, 563–568
indications for, 468
medical management and "do nothing," 563
methods compared, 691–700
modalities, influence of evaluated, 8
understanding of, approaches to, 281
untreated disease, natural history availability, 3
variation in course of, 713
vascular pressure ratios in, 657–663
venous occlusion in, 49
visual impairment, as a cause of, 41–46, 97
visual loss causes in 200 eyes tabulated, 85
visual prognosis, XIX
vitreous studies in photocoagulation, treated with 559–562
what goes on in diabetic retinas?, 651
yttrium-90 implantation, treated by, 317–329
Diagrams of retinal changes useful, 9
Diathermy scars, 582
Diathermy—retinal detachment, for, 619
Di Chiro, G., 373
Diet in diabetic retinopathy, 180, 563, 644

Digital system used for patients' data recording, 256
Dilantin, 361, 397
craniotomy, following, 335
toxic reactions from, 420
Dilated pupil, the examination of, 441
Dilatation, generalized, not an irregularity?
Dilatation, venous, 13
classification of, 13
Diphenylhydantoin, 230
Disk and macula, involvement of, 18
Disk, elevation at the, 29, 30
"Disk vessel leak", evaluation category, 445
Discrete patches, number of in O'Hare classification, XXII, XXIII, XXIV
Discussion
classification, on, 23–37
medical aspects of pituitary ablation, of, 400–413
ocular aspects of pituitary ablation, of, 380–393
photocoagulation treatment techniques, of, 630–653
surgical aspects of pituitary ablation, 422–434
283-patient photocoagulation series, 528–534
Disulphide and sulfhydryl linkages, 680
Ditzel, Jorn, 191, 288, 494, 567
Diuretics
arteriolar occlusion, and, 101
macular edema, and, 101
Dobree, John H., VII, X, XIII, XV, 26, 55–64, 93, 386, 479–484, 609, 610, 615, 617, 620, 623, 639, 641, 644, 646, 663, 689, 692, 694, 699, 702, (Data) 773–777
Dolger, Henry, 115, 117
Dollery, Colin T., VII, 65–79, 70–78, 128, 169, 191, 445, 452, 463, 553
Dominguez, J. M., 729
Donner Pavilion, the, 281
Double blind study, 27
Doyle, F. H., 729
Draper, G. J., 79, 85, 113, 117, 128, 288, 477
Drowsiness or stupor—appearance of, abrupt, 363
Drusen, multiple, in patient without diabetic retinopathy, 165
Duane, Thomas, D., IX, XII, XIII, XV, 28, 169, 203–212, 216, 220, 225, 646, 650, 651, 652, 657–663, 724, 729, (Data) 739–742
Duke-Elder, S., 64, 151, 663
Duncan, G. G., 115, 117, 354
Duncan, L. J., 728
Dunlop, D. M., 115, 117
Dye, fluorescent
see Fluorescein
Dynamics—retinal circulatory, 657

E

Eales' disease, 472
Economic difficulties of diabetic retinopathy patients, 555
Edema
cerebral, 201, 363
pituitary ablation and, 179
continuing, depressing macular function, 100
cotton-wool spot, in a, 101
diminution following hypophysectomy, 306
macular, 85, 468
grading of, 18,
diuretic, and a, 101
laser treatment, and, 603, 605
retinopathy, circinate or, 643–644
postoperative, 361
retinal, 12, 13, 19, 50, 577, 582, 588, 641
disappearance a sign that treatment is adequate, 594–595
recognition of, 14
stalk section, clearing after, 314
ruby laser photocoagulation in, 461
vitreous
disappearance following pituitary ablation, 245
Eggleston, C., 311
Eichhorn, F., 310
Eight-year PDR survey—conclusions from, 63–64
Eight-year photographic survey of lesion evolution, 55–64
Eisner, G., 169
EKG changes, 361
Electrodes, radiofrequency pituitary ablation, in, 370

Electroretinography
see ERG
ERG
conclusions, 688
juvenile diabetics in, a prognostic study, 681–689
hypernormal oscillations, 685
material and methods, 681–682
prognostic value of, 688
proliferative diabetic retinopathy, in, 684, 687
results, 682–688
Elevation, retinal, 12
Elliott P. Joslin Research Laboratory, Harvard Medical School, 153, 171, 437
Emotional adjustment and pituitary ablation, 396
Emotional disturbance in juvenile diabetics, 557
Emotional equilibrium of patients related to success of treatment, 406
Encephalopathy, 292
hypertensive, blindness, and, 265
Endocrines
see also Hormones
endocrine ablation significant following radiofrequency coagulation, 211
replacement therapy following cryohypophysectomy, tabulated, 367
response measurement in a stress test, 400
status appraised, serially, 417
status spectrum achieved by yttrium-90 implants, 318
suppression by pituitary ablation, 203
target gland function persists after pituitary ablation, 163
Endocrinologic evaluation, 174
Endocrinological assays, postoperative, 245
Endocrinological evaluation of patient for cryohypophysectomy, 343
Endocrinologists, 147, 538
Endothelial wall, normal retinal vessels having a remarkable, 159
Engel, M., 169
Engerman, Ronald L., VII, 47–53, 117
Enucleation—glaucoma, for, 313
Epilepsy, nonoccurrence following hypophysectomy, 308
Epilogues, 713–729
Epistaxis, 336
nasal turbinate damage, following, 345
Equatorial area and "white line" illustrated, 62
Erythromycin, 205
Esmann, V., 53, 78
Esophageal varices, ruptured, 271
Estrogen
see also Hormones
Estrogens, 367
androgen replacement, and, 230
replacement estrogen following pituitary ablation, 207
Evaluation of patient in diabetic retinopathy, V
Evans and Long's experiments, 148
Exacerbations, spontaneous, V
Examination
biomicroscopic, 13
minimal, classification and, 34
ocular, in diabetic retinopathy, 469
Exposure of pituitary gland in ablation surgery, 196, 197, 198
Extraocular motor function (EOM), proton beam pituitary suppression. following, 272
Extraocular nerve palsy, 429
Exudates, 442, 570
see also Cotton-wool spots
decreased, illustrated, 587
fibrous proliferation, and, 722–723
fundus photography, showing in. 578–591
Hammersmith studies, in, 123, 124
hard, 3, 21, 49, 50, 318, 472, 607
appear and disappear at random, 327
classification of, 11, 12
pattern of, 466
photocoagulation, and, 577
illustrated, 580
microaneurysms and hemorrhages, patients' comparison, 97
photocoagulation, and, 612, 613
spontaneous resolution of, 631
visual prognosis, and, 41
worsening of, 126

Eye
changes in
fluorescein photography, and, 153–154
diabetic and nondiabetic studies on, various, report of, 673–680
evaluation, pituitary ablation, following, 174
"eye grades", 5
changes in, spurious, 5, 6
eye grading, 34
serial assessments, and, 6
eyeball, schematic sagittal section of, 634
prolongation of life of affected, 528
status—pituitary ablation, following, 183
treatable, yttrium-90, and, 319

F

Factors found not related to success of photocoagulation treatment, 512
Fager, Charles A., VIII, XV, 172, 191, 193–202, 247, 276, 415, 418, 420, 421, 422, 426, 432, 462
Failures, due to inadequate hypopituitarism, 267
Falkheden, T., 311
Feeney, L. ,476
Ferrer, O., 168
Fever, postoperative, 361
Fibrosis, photocoagulation, ascribed to, 611
Fibrous band, inactive, illustrated, 165
Fibrous proliferation, 12
see also Proliferation, 21
extending into the vitreous, XXI, XXII, XXIII
following pituitary ablation, 187
Fibrous retinitis proliferans, 6
Fibrous tissue
development, 93
symbol used to describe, 28
Fibrovascular fans, 594
Fibrovascular tissue, thickening of, 51
Field defects, patients not aware of, 780–781
Field, Richard A., VIII, IX, X, XII, XIII, XV, 28, 94, 147–151, 174, 191, 195, 202, 203–212, 213–225, 247, 252, 272, 275, 276, 281, 289, 342, 353, 354, 355–364, 365–373, 383, 384, 391, 393, 395, 398, 417, 421, 425, 426, 428, 568, 648, 651, 652, 657–663, 692, 695, 700, 715, 717, 722–729, (Data) 739–742
Fine, Stuart L., VI, XX, XXI, 7, 23, 718
Fischer, F., 60, 64
FITC insulin's binding capacities varied from structure to structure, 673
Flat-holes, 57, 58
retinal, detachments, and, 60
Flicker fields and dark adaptation studies, 458
Flocks, M., 442, 462, 671
"Florid" retinopathy, 9
Fluid problems, pituitary ablations, following, 421
Fluorescein
abnormal structures destruction, aids in, 595
aids in heat absorption in photocoagulation, 594
angiography, 9, 47, 65, 167, 174, 596
before pituitary implant, illustrated, 384
evaluation, 14
further refinement of and experience with, 48
hypophysectomy comparison with photocoagulation, and, 615
illustrated, 68, 69, 70, 71, 74
shunt and capillary closure, and, 102
category, "too much emphasis on", 29
changes—classification preferences, 18
circulation, observation of theoretical conclusion, and an, 600
fluorescein-isothiocyanate conjugated insulin, 673
fluorescein-tagged globulin extracted from diabetic serum, 673
fundus angiography, 9
importance of, 713
intravitreal vessels destruction, and, 550
leakage, 14, 389, 390
absorption of photocoagulative energy, and, 547
minimum classification on, 36
pattern of elevated rete at disk with extensive "leakage" of dye, 460

Fluorescein—Continued
permeability of vessels to, 167, 380
pertinent pathology, may reveal more of, 545
photography, 216, 408
advantages of, the, 167–168
aid in considering patients for hypophysectomy, 167
arrested case illustrated by, 165
capillary closure, and, 157
diffusion of dye correlated with activity and severity of retinopathy, 159
early arterial phase illustrated, 597
early arteriovenous phase illustrated, 597
equipment used in, 154
fluorescence obscures rete mirabile, illustrated, 156
highly vascular tissue in, illustrated, 158
hypophysectomy, following, 166
late arteriovenous phase illustrated, 598
leakage diffusion detailed, 154
method detailed, 154
neovascularization and diffuse angiopathy illustrated, 164
neovascularization from disk and diffuse angiopathy illustrated, 162
neovascularization, in, 157
nontraumatic method, a useful, 168
ophthalmoscopic view, compared with, 157
pituitary ablation, following, summary, 168
post-venous phase illustrated, 598
proliferative diabetic retinopathy treated by pituitary ablation in, 153–169
rapid diffusion of fluorescein illustrated, 155
rapid diffussion of fluorescein in vascular tissue, 158
results in patients treated with pituitary ablation, tabulated, 153
rete mirabile delineated with fluorescein, illustrated, 156
Fluorescein—Continued
photography—continued
retention of fluorescein, 157
ruby laser photocoagulation, in, 441
therapy, after, 159
24-year-old female, in a, illustrated, 163
28-year-old male, in a, 161
vessel permeability, and, 154
potential vitreous hemorrhage, an aid in detecting site of, 519
rate of flow of, 662
solution injection, 14
strength used by Okun and Zweng, 647
studies, 386, 440
preliminary classification, and, 36
radiofrequency coagulation candidates, in, 203
stages of, comparison, 616
treatment adjunct, its value as a, 594, 720
used prior to photocoagulation session, 623
will it show aneurysms not clinically apparent?, 653
xenon-arc energy, absorbs, 647
Fluorescence, microscopic studies on diabetic and nondiabetic eyes, 673, 680
Foley catheters used following stalk section, 362
Followup of 42 cases of radiofrequency coagulation, 209
Followup period, one-year, 32
Form for recording ophthalmoscopic classification of patients, 17
Form for recording photographic classification of patients, 19
Forrest, A. P. M., 202, 230, 234, 339, 373, 416
Francois, J., 68, 688
Frantz, A. G., 729
Fraser, T. Russell, VII, VIII, IX, X, XIII, XVI, 119–128, 3–6, 134, 139, 233, 317, 373, 398, 400–413, 416, 424, 426, 434, 619, 643, 729, (Data) 731–738
Friedenwald, J. S., 79, 288
Friedman, Ephraim, 671
Fronds, neovascular, 4

FSH "may be only hormone found", 400
Fundus
degrees of, photographed, 35
detailed drawings of, 26, 507
diagrams, 9, 81, 229, 721
pallor of the, 61
photographs, *see also* Photography *and* Classification
photography, 3, 8, 18, 33, 47, 81, 342, 348, 349, 578–591, 713
camera, 34
changes after photocoagulation, 720
classification, importance in, 8
eminent importance, of, 577
photocoagulation, following, 438
postoperative, 208
stereoscopic, 52
stereoscopic type desirable, 9
Funduscopic examination in patients before and after pituitary ablation, 333
Fung, W. E., 468, 477, 632
Fusiform aneurysms, 9

G

Galactorrhea, 208
Gangrene, 271, 292
Garcia, J. F., IX, 277–289, 715
Garrett, C. J., 45, 234, 339, 567
Gastineau, C. F., 191, 276, 353, 494
Gastritis, bleeding, 271
Gay, A. J., 477, 663
German Ophthalmological Society, 569
Giantism, 148
Glaser, J., 7
Glaucoma, V, 17, 30, 241, 262, 264, 265, 315, 388, 390, 469, 473, 540, 565, 658, 660
advanced, 530
glaucoma-associated rubeosis, 387
hemorrhagic, 85, 307
preoperative, blindness, following, 389
rubeosis iridis, with, 58, 513
secondary, 57, 63, 518, 527
photocoagulation, after, 572
Gliosis, 292
reactive, 466
Glomerulosclerosis, 232
diabetic, 233
Glucagon, 180
Glucose
disappearance rate change with intravenous insulin, 410
renal threshold for, 556
Glycosuria
degree of, retinopathy and, 130
insulin in treatment, 110
percentage, 107, 111, 112
chances of development of retinopathy, age, and, 109
changes, data on, 136
charted, 109
frequency of retinopathy 10 to 14 years after diagnosis of diabetes, and, 111
mean of blood sugars, charted, and the, 108
retinopathy frequency and, 107
rates, significance of, 714, 715
threshold for, 120
Gold implantation, 565
Gold, Joan, IX, XIII, 341–354
Gold plate interposition is stalk section, 356
Gold plates and gold foil used in pituitary ablation, 415
Goldberg, Morton, F., VI, XX, XXI, 7, 23, 718
Goldmann applanation tonometer, 294
Goldmann perimeter, visual field at the, 572
Goldmann projection-perimeter, 293, 303
Goldmann three-mirror lens, 293, 441
Gonadal function tests following pituitary ablation, 333–334
Gonadal replacement therapy following pituitary ablation, 179
Gonadotropic function evaluation, 203
Gonadotrophins, 223, 726–727
assessment of, 242, 243
deficiency, of, 318
Gonads, investigation, 242
Gordy, P. D., IX, X, XII, 203–212, 365–373, (Data) 739–742
Gorn, R., 53, 671
Grading definitions tabulated, 12–13
Grading eyes, 5
Grading lesions of, 11
Grading by photography, 21, 22

Granular blood flow in diabetic retinopathy, 49
Graves' disease — hypophysectomy, total, after a, 404
Greenberg, Ernest, XIII, XVI, 227–234, 392, 405, 407, 419, 653, 729, (Data) 743–747
Group categories of patients receiving ruby laser photocoagulation treatment, results in, 446–453
Group classification of signs related to prognosis in response to ruby laser photocoagulation, 440
Growth hormone—presence with other hormones, its, 403
Guide dogs, blind diabetic individuals, and, 87
  useful life of, 87
Guillaumat, L., 592
Guinan, P., 506
Gutman, F., 168, 477, 663

H

Hagg-Streit 900 slit lamp for vitreous examination, 293, 559
Hall, W. A., 729
Halvestadt, D. B., 363
Hamberger, C. A., 311, 415
Hammersmith Hospital, London, England, 119, 317, 702
  classification, five grades and four photographs in, 24
  grading system of, 121
    nonstereoscopic fundus photographs in, 6
    O'Hare system, compared with, 29
    Ophthalmologists and diabetologists using the, 3
    standard photographs availability in, 3–4
    validity of the, 3–4
  Hammersmith group, the, 28, 29, 33, 376, 337, 420
    findings of, 93
  physicians from, 652
  study of, 119–128, 130, 727
Hand signals by patient in cryohypophysectomy, 344
Hanley, John, IX, XIII, 341–354
Hard exudates
  see Exudates, hard
Hardin, R. C., 115, 117, 119, 128
Hardy, Jules, IX, XIII, XVI, 195, 196, 202, 235–247, 276, 332, 339, 353, 376, 378, 396, 410, 411, 415, 418, 420, 429, 430–431, 692, 695, 700, 703 (Data) 748–750
Harris, Gordon S., X, XIII, XVI, 485–494, 609, 624, 692, 695, 700, 703, (Data) 778–779
Harrold, B. P., 310
Hartford Foundation, John A., 153
Hartog, M., IX
Harvard group, The, 416
Harvard Medical School, Boston, 171, 213, 275, 665
Harvard Physics Laboratories, 275
Hazards minimal in photocoagulation, 593
Health, general, photocoagulation, and, 593
Heart
  failure, congestive, 426
  heart-beat monitoring during stalk section, 356
  tests on following hypophysectomy, 300, 308
Heavy particle pituitary suppressive therapy
  see Pituitary suppression
Heavy particle radiation, 395
  therapy survival statistics, 279–281
Hedges, T. R., 53
Henkes, E., 681, 689
Henkin, Robert, 191
Hematoma, postoperative, 361
Hemianopia, 490
  altitudinal, 491
  transportal ablation, following, 420
Hemodynamics, retinal, 167–168
Hemoglobin
  evaluation, 299
  photocoagulation by ruby laser, and, 604, 605
Hemorrhage, XXII, 3, 232, 253
  angiopathy, and, 186
  blindness, causing, 417
  blood pressure readings, and, 126
  choroidal, 57, 58
  classification, preventing, 31
  disappearance following pituitary ablation, 245
  freedom from in retrogressive stage, 60–61

Hemorrhage—Continued
fundus photography, shown in, 585, 588
grading of, 11
grading of, yttrium-90 implant, following, 322
hemorrhagic glaucoma, 307, 308
hemorrhagic lesions classified, 16
intraocular, prevention of, 546
intraretinal, 313
intraseller, epistaxis, and, 336
macular, 26, 85
manifestation of progression of retinopathy, a, 596
massive, 571
microaneurysms, and, 123
Hammersmith studies, in, 123, 124
patients comparison, 97
new, photocoagulation, in, 572
ocular recurrent, 468
orbital, following anesthetic injection, 490
photocoagulation, before and after, 542–543
photocoagulation for, 649
preretinal, 13, 21, 167
prevention by photocoagulation, 612
punctate, 277
recurrent photocoagulation preventing, 569
recurring in spite of improving angiopathy, 260
retinal, 109, 306
angiopathy, hemorrhagic, 171
pituitary ablation for, 203–212
visual prognosis, and, 41
small, illustrated, 578
spontaneous, 451
subhyaloid, 57, 58, 60, 607, 608
treatment of, 547
"swallow's nest" type, 57
traction type, 721
treatment of recurrent, 542
visual acuity, and,
see Visual acuity
vitreous, XXI, 13, 43, 57, 58, 315, 352, 513, 518, 607, 608
discovery of, 36
history of, 16
photocoagulation, ascribed to, 611, 618
preretinal, and, 437
Hemorrhage—Continued
vitreous—continued
prognosis after, 43
reason for, the major, 650
ruby laser photocoagulation, and, 452
severe, 85
site of origin or, illustrated, 628
vitreous traction causing, 624
Hepatitis, 230
Hernberg, 722, 728
Heuser, Gunnar, IX, XIII, 341–354
Hill, David, 168, 174, 329, 729
Histochemical studies, 673–680
Histological examination of removed pituitary, 243
Histology of the pituitary, 243, 244
Histopathologic changes, disagreement as to sequence of, 47
Histopathologic studies agreement, 47
Histopathology, laser coagulation, of, 637
Hirose, Kinnosuke, 53, 688
Hirsch, Oscar, 148
Hodge, J. V., 70, 78, 169
Hogan, M. J., 466, 476
Hollenhorst, R. W., 53
Hormones
see also Endocrines
ACTH, 411, 716
ADH secretion, 406
adrenal steriod excretion tests, 285
adrenal steroids, 347
androgen and estrogen replacement, 230
androgens and spermatogenesis, 407
antidiuretic, 405
effects of, 274
estrogen, 402
evaluation of endocrinological status of candidates for cryohypophysectomy, 343
"FSH may be only hormone found", 400
gonadotrophins, 726–727
growth hormone, 726
assays, 281, 282
levels altered by hypophysectomy, 277
persistence and retinal deterioration, 401
pituitary ablation, and, 542

Hormones—Continued
growth hormone—continued
presence and other hormones, 403
release blunted, 715
response to hypoglycemia, 398
secretion and its role, 287
studies, 410
hormonal pituitary mechanism in pathogenesis of diabetic retinopathy, 235
hormonal versus neural pathogenic mechanism hypotheses, 235
incorrect balances of, 412
insufficiency, hormonal, 235
levels testing by radio immunoassay measurements, 334
lipotrophic, 245
measurement of, 400
pituitary direct assay unavailable, 242
replacement therapy, 411
substitution after hypophysectomy, 308
suppression, hormonal, 563, 564
Horsley's experiments, 148
Horton, G., 53
Hospitalization
convalescence avoided by pituitary suppression, and, 249
pituitary suppression, in, 249
Houssay and Biasotti, 291
Houssay and pituitary function, 149
Houssay, B. A., 310
Houssay's phenomenon, 235
Houtsmuller, A. J., 689
Howard, G. M., (Data) 820–827
Howe Laboratory of Ophthalmology, 665
Hruby lens classification, 36
slit-lamp biomicroscopy, in, 8
Humphrey, M. J., 310
Hyaline degeneration of hilar glomerular arterioles, 224
Hyaloid membrane, degeneration of, 499
Hydrocortisone, 205, 207, 239, 362
Hydroxycorticosteroids test, 174
Hyperadrenocorticism, 277, 278
Hypercholesterolemia, persistent, 445, 446
Hyperglycemia, insulin in treatment of, 110, 230
Hyperpituitarism, 148
Hypertension, 253, 426, 445
diastolic, 177
control of, 175
hypophysectomy, and 332
remediable sources of, 174
severe, 229
Hypoglycemia, 180, 188, 207, 217, 402, 409, 416, 417
arginine test for, 402
death from after pituitary ablation, 194
frequent, fat loads, and, 140
growth hormone response to, normal, 318
insulin-induced, 400
insulin type
growth hormone response, and the, 283
pyrogen test for, 402–403
Hypokalemia, 207
Hypometabolism, serum creatinine and blood urea decrease consequent on, 309
Hyponatremia, 188, 210, 321, 405
hyponatremic syndrome, postoperative, 404
pituitary ablation, 179
surgery after, 397
Hypophyseal capsule, identifying the, 236
Hypophyseal stalk section
see Stalk section
Hypophyseal suppression, metabolic changes, and, 282–285
Hypophysectomy, 88, 89, 153, 563, 564
see also Pituitary ablation *and* Pituitary suppression
age of average patient undergoing, V
amelioration of diabetic lesions largely "a vain hope," 720
Bragg proton beam type, 252
cancer of the breast, in, 236
completeness important, 337
completeness of, 333–334
desirability of, 422
diabetic angiopathy a controlled clinical trial, for 291–311
diabetic angiopathy's spontaneous course, and, 291
diabetic retinopathy in 1936, for, 149

Hypophysectomy—Continued
endocrinological parameters in 30-patient series, 296
evaluation of widespread, 341
extirpative, stress, surgical, imposing, 341
fluorescein photography, showing result of, 166
heavy-particle radiation, by 277–289
hypophysectomy frame, 370
hypopituitarism not guaranteed by, 183
illustrated, 238
improvement following, 172
kidney, beneficial effect on?, 391, 392
less insulin needed after, 241
methods of, various, 235
not beneficial for almost sightless patient, 228
"not sure how it acts," 387
nonrandomized studies, 723–724
organs benefiting?, 291
patients considered for, 100
five-year spontaneous course of, 100
patients with large insulin requirement, 141
photocoagulation after, 648
pituitary stalk section compared with, 171
pituitary suppression by proton beam an alternative procedure, 249
post-mortem systemic findings, 722
pregnancy after, 726
results, in 52 cases summarized, 338
results of, tabulated, 336
retinal vascular disease, in, 723
rubeosis, and, 387, 388
Johns Hopkins Hospital, series at, 566
sexual drive and potency after, 309
subtotal type, 173, 395
surgical, 565
medical management of, 334–335
relatively safe and effective, 201
stalk section and irradiation survival rates compared, 280
technical observations on, 193–202
techniques of, 331–332
36-year old male, in a, 162
total type, 173
Hypophysectomy—Continued
total—value compared with other type of ablation, 727
transsphenoidal, 294, 395
"not a dangerous operation", 307
open, 252
results in 30-patient series, 295, 296
28-year-old male, in a, 161
vascular parameter in 30-patient series, 296
visual improvement after, 241
vitreous clearing following, 383
"what are the specific effects of?", 387
"what does it do to the eye?", 380
"when should it be performed?", 292
"why are benefits confined to the eye?", 390
Hypophysis, approaches to, 365
Hypopituitarism, 148, 220
control observations of, lack of, 278
degree following pituitary ablation, tabulated, 183, 184
"grim predicament, a", 193
heavy particle radiation and, 149
heavy particle radiation produced by, 277–289
hypopituitary state, hazards of the, 188
not guaranteed by hypophysectomy, 183
onset-of, rapid, 278
patient failures due to inadequate, 267
pituitary ablation, and, 171
production of in diabetes treatment, 722
Hypotension, orthostatic, following hypophysectomy, 309
postural, 188, 445
retinal arteriolar, 659–660
systemic, 661
yttrium-90 implant, following 328
Hypothalamus—fibers running from retina to the, 410
Hypothalamus and the centrifugal fibers in the optic nerve, 235
Hypothetical retinopathy poll at symposium, 652
Hypothyroidism, 188
Hypotony, ocular, 658, 660

Hypovolemia, 362
Hysterical patients, note on, 406

I

IBM sorter and punch cards used for patients' data, 256
Identifying card warning that holder has hypopituitarism, 397
Igersheimer, J., 663
Image intensification and counting devices, 33
Immune process damaging retina of other eye, questioned, 615
Impaired vision, cataracts causing, 88
Impairment, visual—diabetic retinopathy as a cause of, 41–46
Impotence, androgen therapy for, 407
Iodine-125 labeled insulin, 673
Incidence of preoperative and postoperative findings in photocoagulation patients 541
India-ink injection, 61
Incisions in stalk section, 355
Infarction
  gland in inconsistent state of, 433
  ischemic, 49
  myocardial, 190
  spontaneous, 277
    pituitary, of the, 341
Infection, chronic ineradicable, 177
Infertility, 178
Innes, J. A., 291, 310
Institute of Ophthalmology at Columbia-Presbyterian Medical Center, 545
Insufficiency, vascular, 52
Insulin
  administration of, 180
  alteration of type of regimen, 135
  chronological changes in requirement following pituitary ablation, 409
  diabetes treatment at Hammersmith, in, 123
  insulin-iodine-125 binding over newformed vessels in diabetic retinopathy illustrated, 678
  immediate acting, 205
  production and effect, 408
  reaction deaths, 272
  response to, 408
Insulin—Continued
  requirements, hypophysectomy, and, 141
  sensitivity to, 177, 716
Intelligence of patient and pituitary ablation, 229
Intensity of photocoagulation therapies tabulated, 510
Interference with nutrient vessels to ocular apparatus to be avoided, 430
Internal Medicine, XIX
International symposium steering committee, VI
International symposium, value of, V
Internists, 147, 150, 564
Intraocular pressure and asymmetry in diabetic retinopathy, 660, 661
Intraocular tension, 307
  determination, 294
Intraretinal arterial pressure measurements, importance of, 651
Intraretinal leakage illustrated, 15
Intraretinal microvascular abnormalities, 13
Intravenous studies, 65
Intravitreal hemorrhagic lesions, 16
Intravitreal volume reduction, 633
Intubation of patients, 428
Ireland, J. A., 352, 354, 399, 722, 728
Iris, the, illustrated, 675, 677
Iritis, 599
Irradiation
  See also Radiation therapy
  heavy-particle type, 173
    pituitary ablation, following, 173
  insulin requirements following, 409
  neutron-beam type, 229
  procedures less stressful, 421
  proton beam type, 153, 204, 393, 395
    fluorescein photography, following, 164
  pituitary—growth hormones, and the, 282, 283
  therapy, stalk section and surgical hypophysectomy survival rates compared, 280
  reviewed, 715, 717
Irregularities, venous, 5
Irreversible eye described, 319
"Irreversible eyeball," the, 26
Isaacs, M., IX, XIII, 227–234, (Data) 743–747

Ischemia, 47, 48, 607, 639
cerebral, 360
transfrontal ablation, following, 420
diabetes mellitus leading to, 468
generalized retinal, 85
hard exudate and retinal edema related to, 50
infarcts, 49
ischemic disturbance of neurohypophyseal track, 244, 245
myocardial, 418
death from, 418
neovascularization and, 52
pathogenesis of diabetic retinopathy, role in, 51
photocoagulation eliminates ischemic areas, 616
Ishihara color vision tables, 682
Isodose curve in proton beam pituitary suppression, 251

J

Jackson, C. C. R., IX, LXIII, 331–339
Jacobson, J. H., 681, 688
Judresic, A., 365, 373
Jain, I. S., 477
Jane, John A., IX, XIII, LVI, 331–339
Jaqua, R. A., 225
Jaundice, 348
Jefferson Medical College of Philadelphia, 203, 216, 224, 657
Jensen, Viggo, A., IX, 291–311
Jepson, C. N., XI, XIII, 462, 477, 488, 514, 535, 543, 568, 592, 593–601, 609, 624, 698, 700, 714, (Data) 828–851
John A. Hartford Foundation, 437, 665
Johns Hopkins Hospital, Baltimore, Md., 367, 378, 564
pituitary procedures at, tabulated, 565
Johnston, Glen Paul, XI, XIII, XVI, 7, 23, 523–535, 609, 610, 624, 696, 700, 714, (Data) 787–816
Jonsell, S., 310
Joplin, Graham F., VII, VIII, IX, XIII, XVI, 3–6, 24, 25, 28, 119–128, 136, 194, 202, 208, 234, 310, 317, 329, 339, 351, 353, 377, 378, 401, 416, 421, 423, 424, 649, 714, 719, 723, 728, 729, (Data) 731–738
Joseph M. and Evelyn R. Weidberg Foundation, 437
Joslin Clinic, the, 153, 171, 178, 275, 279, 280, 437, 441, 462, 725
Joron, G. E., 567
Journal of Neurosurgery, the, 428, 430
Jules Stein Eye Institute, 341, 537
Jutte, A., 168
Juvenile diabetics, ERG in, 681–689
see ERG

K

Karpe, G., 681, 688
Karpe's contact lenses, 682
Katsuse, T., 567
Kaufman, B., IX, XIII, 331–339
Kearns, T. P. 53
Keeler ruby laser, 637
Keen, Harry, XVI, 27, 28, 135, 615
Keiding, N. R., 119, 128
Keratitis, 599
Ketoacidosis, diabetic, 140
Ketosis, diabetic, 109
17–Ketosteroids 24-hour excretion test, 174
Kidney
function remains stable after cryohypophysectomy, 352
hilar arteriolar changes in, 395
insufficiency tests, 308
kidneys "don't get better", 390
tests on following hypophysectomy, 296, 300, 308
King, R. C., 567, 641
Kjellberg, Raymond N., IX, XII, XIII, XVI, 249–276, 375, 377, 378, 388, 389, 396, 398, 401, 402, 410, 416, 418, 424, 425, 426, 432, 691–700, 703, 715, 717, (Data) 751–761
Kjellberg, S. R., 310
Kling, R., IX, 277–289
Klinische Monatsblatter, the, 569
Kloti, R., 51, 53
Knoblich, R. R., 247, 354, 727, 729
Knowles, Harvey C., Jr., VIII, XVI, 113, 115–118, 129–131, 134, 140, 141, 143, 650
Knox, David L., 564
Kodachrome II film, 121
Kodak Tri-X film, 154
Koehler, Andreas M., IX, XII, XIII, 249–276, 378, 379, 691–700, 715, (Data) 751–761

Kohner, Eva M., VII, VIII, IX, XIII, XVI, 3–6, 7, 27, 29, 31, 34, 35, 65–79, 100, 101, 102, 119–128, 129, 130, 132, 133, 134, 136, 137, 138, 139, 140, 141, 143, 169, 317, 380, 386, 389, 390, 391, 416, 612, 643, 652, 703, 714, 715, 726, 729, (Data) 731–738
stipulation of, hypothetical, 652
Kojima, K., 681, 688
Koren, B. J., IX, XIII, 227–234, (Data) 743–747
Kornerup, T., 119, 128, 663, 688
Kuwabara, Toichiro, XII, 53, 169, 463, 476, 665–671

L

Lahey Clinic, the, 172
Lammens, A. J., 169
Lanthier, Andre, IX, XIII, 235–247, (Data) 748–750
Larsen, Hans-Walther, X, XII, XVI, 30, 495–506, 609, 618, 673–680, 703
Larsson, H., 310
Laser
coagulation, histopathology, 637
coagulator used at Columbia-Presbyterian Medical Center, 552
march across the retina with, 639
Optics Technology type, 523
photocoagulation, 603–605, 615
apparatus for, 547
usefulness at present uncertain, 603
retinal bombardment by, 644–645
ruby type, 637
monkey experiments, in, 665–671
photocoagulation, by, 437–463
treatment
no anesthesia required in, 623, 645
xenon arc, and, 636, 637
value of, the, 714
Lauritzen, E., 168
Lawrence, John H., IX, 202, 277–289, 353, 416, 715
Lawrence Radiation Laboratory at University of California at Berkeley, 277
Leadbetter, G. W., 363
Leakage from disk area—photocoagulation, after, 615, 616
Leakage of disk vessels photocoagulation, and, 452
Lee, P. F., 22, 64, 247, 467, 477, 494, 507, 514, 562
Legal blindness defined, 30
Lemke, L., 168
Leopold, Irving H., XI, XVI, 612–622
L'Esperance, F. A., Jr., 442, 462, 568
Lesion, arteriolar, 221, 222
destruction by photocoagulation—"shooting sparrows with a cannon," 556
duiretics, response to, 101
evolution, 8-year photographic survey of, 55–64
grading into three divisions, 11
grading tabulations, 12–13
grading types of, 9
hemorrhagic, classified, 16
location of, macula, and the, 27
prognosis, and, 27
visual acuity, and, 26
pathologically varied, are, 115
photocoagulation, in, 443
prevention of progression of, 127
regression on low fat diet, 115–116
sequence in P.D.R., 55
severity of, 24
vascular, treatment of, 630
which are reversible by photocoagulation?, 620
retinal—which should be treated by photocoagulation?, 547
Lester, Harvey, XVI
Levene, R., 53
Libido
diminished, 178
hypophysectomy, following, 309
retained after pituitary ablation, 207
Lichtenstein, A., 115, 118
Light coagulation, 479–484
See also Photocoagulation
as an adjunct to cryohypophysectomy, 537–544, (Data) 773–777, 817–819
diabetic retinopathy, for, 479–484
review of 232 patients, 593–601, (Data) 828–851
Light reflex, increase in, 50

Linfoot, John A., IX, XVI, 23, 24, 277–289, 386, 393, 398, 403, 407, 416, 425, 653, 715, 725, 728
Linde cryoprobe, 343
Lipid complex, circinate, illustrated, 642
Lipid formation, 641
Lipid intake and plasma lipids, 115
Lipid reabsorbed after photocoagulation, 641, 642, 643
Lipotrophic hormones, 245
Lopez, de Andrade, A., 592
Low fat diet and lesion regression, 115–116.
L-thyroxine, 207
Luft, R., 177, 191, 212, 227, 247, 291, 310, 311, 331, 339, 341, 353, 395, 399. 722, 728
Lundbaek Knud, VIII, IX, XVII, 30, 36, 46, 53, 78, 129, 132–144, 139, 140, 141, 143, 149, 291–311, 339, 351, 354, 376, 378, 387, 388, 389, 390, 403, 404, 405, 407, 415, 613, 643, 650, 653, 716, 724
Luthra, C. L., 477
Lyall, A., 291, 310

M

Macrophage function may be abnormal in diabetes, 76
Macula
  degeneration after photocoagulation, 518
  detachment of, 85
  displacement of, 59
  inadvertent coagulation of, 551
  location of lesion, and, 27
  macular burns in photocoagulation, 599
  macular changes, 30
  macular lipid and extramacular coagulation, 612
  macular pigment, 85
  macular vision
    in at least one eye prerequisite for stalk section, 313
    retention, 211, 542
  maculopathy, 720
Madsen, Poul Henry, IX, 53, 78, 291–311
Magli, Yvonne L., VII, 47–53, 81–85
Male more susceptible to angiopathic retinopathy, 222
Malmros, Richard, IX, 291–311
Management, medical—hypopituitarism, in, 278
Manougian, E., IX, 277–289
Marback, E. P., 310
Marble, Alexander, VII, 115, 117, 128, 153–169
Marchildon, André, IX, XIII, 235–247, (Data) 748–750
Margolin, Morris, 46
Margolis, M., 169
Massachusetts Eye and Ear Infirmary, Boston, 213, 215, 510, 620
  Retina Service of, 559
Massachusetts General Hospital, 213, 275, 395, 396, 398, 401
Massachusetts Lion's Eye Research Fund, 171
Massachusetts State Grange, 437
Matson, Donald D., 172
Mayo Clinic, the, 418
McDonald, Glen, XX
McManus, Nancy, IX, XIII, 249–276, 715, 751–761
McMeel, J. Wallace, X, XI, XII, XIII, XXI, LVII, 7, 23, 28, 32, 100, 174, 188, 213–225, 249–276, 313–316, 375–379, 385, 506, 507, 514, 559, 609, 620, 614, 615, 618, 619, 624, 630, 631,635, 644, 646, 648, 691–700, 703, 709, 715, 717, 724 (Data), 751–761
Medical aspects of pituitary ablation
  discussion of, 400–413
  summary of papers on, 395–399
Medical evaluation of patients before ruby laser photocoagulation, 445
Medical Foundation of Metropolitan Boston, 249
Medical Management and "do-nothing," tabulated, 563
Medical management in pituitary ablation, 717
Medical Research Council (British), 78
Medical status, general—data needed on, 23
Membrane formation—photocoagulation, ascribed to, 611
Memorial Sloan-Kettering Cancer Center, 277

Meningitis, 194, 195, 211, 321, 419, 420
bacterial, following hypophysectomy, 295
death from, 307
pituitary ablation, following 208, 231
radiofrequency ablation, following 371
Menses
cessation of, 403
menstrual activity changes, postoperative, 210
menstrual responses, 267
pituitary ablation, following, 208
pituitary function index, as a, 267
pituitary ablation, and, 182
resumption after hypophysectomy, 726
resumption following postoperative amenorrhea, 221
Mental instability in a patient undergoing photocoagulation, 540
Merrimee, T. J., 289
Methods of classification, validation of, 27–28
Methods of treatment, compared, 691–700
Metabolism
attention to following stalk section, 362
improvement, speculative, 546
metabolic control
diabetic retinopathy, and, 106–144
grades of, 133
interpretation of Kohner's study, 134
relationship to retinopathy, summary of papers, 129–131
retinopathy, discussion of, and, 132–144
metabolic demands of retina, reduction of, 646
metabolic observations following heavy-particle radiation therapy, 277–289
metabolic requirements, lessening photocoagulation by, 639
metabolic studies on 37 patients receiving irradiation, 281, 282–285
retina, of, "no way of getting at it," 651
total metabolic suppression and retinal metabolism, 399
Metapyrone, steroid response to, normal, 318, 416
Meyer-Schwickerath, G., XI, 506, 514, 523, 543, 545, 553, 563, 568, 569–592, 609, 611, 612, 623, 624, 627, 718
Michaelson, I. C., 466, 472, 476
Microaneurysms XXII, 3, 4, 15, 47, 65, 101, 232, 272, 313
area of, illustrated, 67, 68, 69, 70
blood-flow variable, 68
cotton-wool spots, progression to, 101
counts, accurate and reproducible, 72
decrease in leakage from, 380, 381
disappearance of following photocoagulation, 570
disappearance of, interpreted, 167
fluorescein photography, in, 157
fundus photography, shown in, 350, 578, 591
grading of, 4, 11
grading of, yttrium-90 implant, following, 322
hemorrhages, and, 123
diabetes control, and, 126
hemorrhages and exudates, patients' comparison, 97
improvement in demonstrated following complete ablation, 385
laser bombardment of, 645
life history of, 66
multiple, illustrated, 587, 588
not a uniform population, 74
number of, classification of, 11, 12
pathogenesis of, 48
photocoagulation, and, 546, 577
photocoagulation by ruby laser, and, 444
pituitary ablation benefits, 323
plotting diagrammatically, 65
rate of formation of, 74–75
severe, moderately, 49
thrombosed, 157
visual prognosis, and, 41
Microangiopathy, 137
"diffuse", 159
generalized, 172
lacking in patients having diabetes for 30 to 40 years, 144
pancreatic in diabetes, demonstration of, 116

333-611 O - 69 - 58

Microinfarcts, 466
superficial, 13
Microsurgery in pituitary ablation, 235, 236, 238
illustrated, 238
technique detailed, 236–239
Microvascular abnormalities, 9
intraretinal, 12
Microvascular lesions, referrable to diabetes, 426
Microvascular occlusion, 466
Midline puncture occlusion following radiofrequency ablation—rhinorrhea, its effect on, 372
Minkowski and the pituitary gland's function, 148
Mirsky, I. A., 115, 117
Mirsky, Stanley, 191, 288, 567, 494
Miscellaneous topics, 655–710
Mitochondria, enlarged, 668
Monkey retina, ruby laser's effect on, 665–671
Monochromatic green light, 29
Montage, photographic, in classification, 24
Montreal, Canada, University Medical School, 235, 419
Morbidity
dose-related in yttrium-90 implantation, 424
following yttrium-90 implantation, 195
heavy-particle pituitary suppressive therapy, in, 287
modest in proton beam pituitary suppression studies, 275
patient selection, and, 418
pituitary suppression, in, 249
proton beam pituitary suppression, in, 272
stalk section, following, 360–361
Morphologic classification, 32
see also Classification
Mortality
absence of in cryohypophysectomy series, 346
absent in proton beam pituitary suppression studies, 275
heavy-particle pituitary suppressive therapy, in, 287
hypophyseal stalk section, following, 217–218
Mortality—Continued
morbidity, and, 426–427
162-patient study, in, 279
patient selection, and, 418
pituitary ablation, following, 189
pituitary suppression, in, 249
proton beam pituitary suppression, in, 271
stalk section, in, 359
surgical, elimination of, 227
yttrium-90 implants, following, 321
Mortimer, Clive B., XI, XIII, XVII, 515–521, 609, 610, 623, 624, 692, 696, 700, 703, 719, (Data) 782–786
Mortimer's 64-patient photocoagulation series
see Photocoagulation
Motivation of patient a criterion for pituitary stalk section, 362
Moura-Brazil, N., 592
Mydriacyl, 442
Myers, Frank L., VII, XII, XVII, 7, 22, 23, 47–53, 81–85, 94, 701–710
Mylius, K., 592
Myocardial infarction, 177, 190, 217 346
Myocarditis, viral, 208
Myopia, 530
high type, 473
Myxedema, clinical, 403, 404

N

Nakajima, A., 681, 689
National Aeronautics and Space Administration, 249
National Cancer Institute, 227
National Council to Combat Blindness, 437
National Institute of Neurological Diseases and Blindness, 47, 87, 523, 559, 657, 701
National Institutes of Health, 47, 203, 213, 249, 232, 523, 665
Division of Research Facilities and Resources, 701
Natural course of diabetic retinopathy, 321 eyes followed 1 year or more, 81–85
Natural history and visual prognosis, 39–103
discussion on, 99.

Natural history of diabetic retinopathy, 65–79
discussion on, 72–77
summary of papers on, 93–95
Necrosis
ocular nerve, of the, not seen in 2,000 implantations of yttrium–90, 423
pigment, of, in the monkey retina, 666
pituitary fossa floor, of the, yttrium-90, and, 423
sellar floor, of the, 365
yttrium-90 implants, following, 342
Nelson, K. B., 378
Neosynephrine, 442
Neovascular formation warranting photocoagulation, 217
Neovascular fronds, 4
Neovascular retinopathy, severe, illustrated, 454
Neovascularization, 12, 21, 253, 313, 437, 495, 607
abortive attempt at, 48
assessment following pituitary ablation, 174
before and after photocoagulation illustration, 529–534
capillary abnormalities distinctions, and, 4
common feature of, 57
described, 14
diffuse angiopathy illustrated, and, 164
diffuse angiopathy illustrated by fluorescein photography, and, 162
elevated fibrous proliferation, and, 451
eliminated by photocoagulation, 720
illustrated, 530
excessive permeability of new vessels, 51
fluorescein photography showing, 166
grading of, 14–16
grading of new vessels following yttrium-90 implant, 323
illustrated, 529, 530
intraretinal, 9, 10, 13
iris, of the, 6, 7
on and above disk, illustrated, 625
Neovascularization—Continued
pathogenesis of, 668
photocoagulation, and, 577
photocoagulation destroying, 640
photocoagulation will eliminate, 523
preretinal, illustrated, 524
photocoagulation, after, 525
regression from, 60–61
relative proportions of eyes having new vessels on the disk, 57
retina, of the, illustrated, 590
retinal surface, at, fluorescein photography, 159
retinal surface, on the, amenable to photocoagulation, 547
retinal vein occlusion, and, 555
ruby laser photocoagulation, and, 440
sites of vessel origin, 56–57
spontaneous regression of, 466
stimulus for, 159
surface of retina, on the, 49
symbols used to define, 28
temporal to macula, illustrated, 626, 627
treated on appearance, 630
unfavorable prognostic implications of, 51
visual retention index, and the, 242
Nephropathy, 253, 292
evidence of, time incidence of, V
no death from in yttrium-90 series study, 328
pituitary ablation's effect on, 427
retinopathy, and, 555
significant, described, 176–177
Nerve fibers in pituitary stalk, 727
Nerve palsy, yttrium-90 implant, 336
Nervous system
peripheral
tests on following hypophysectomy, 300
test-vibration perception test, 293
Net vascular pressure concept, 657–660
Neural mechanism hypothesis of Wolter, 246
Neural mechanism in pathogenesis of diabetic retinopathy, 235
Neuritis, heat-optic, 518, 519, 618, 624

Neuroendocrine Clinic at UCLA School of Medicine, 342, 537
Neurological and Sensory Disease Control Program, XX
Neurological assessment of patient for cryohypophysectomy, 343
Neurologists, 538
Neuropathy, 172, 253, 292
Neurosurgeons, 147, 150, 277, 538, 564
Neurosurgery, XIX
New England Deaconess Hospital, Boston, Mass., 153, 442, 437, 665
New Orleans Ophthalmology Society Symposium of Retina and Retinal Surgery, 632
New vessels, 3
  grading of, 4
  Hammersmith studies, in, 124, 125
  retina, on, illustrated, 459
Newell, F. W., 476, 543
New York Hospital—Cornell Medical Center, 227
Nikon 35mm camera, 154
Nonocular criteria for patient selection for pituitary ablation, 417–418
Nonrandomized studies, 723–724
Norlen, 415
Norton, Edward W. D., VIII, XVII, XXI, 7, 23, 28, 30, 32, 34, 36, 139, 168, 384, 386, 477, 615, 636, 650, 651, 663
Notre Dame Hospital, Montreal, Canada, 235
Novotny, H. R., 169
Noyori, K. S., 462
Nutrition and the edematous retina, 102
Nutritional deprivation of peripheral areas of retina, 546
Nutritional factors in diabetic retinopathy, 116

O

Oakley, Nigel, W., VII, VIII, IX, XIII, XVII, 3–6, 7, 22, 23, 24, 33, 78, 119–128, 134, 142, 169, 191, 317, 320, 329, 386, 391, 392, 412, 416, 445, 452, 463, 640, 649, 714, 729, (Data) 731–738
Oakley, Wilfrid, 329
Observation technique and classification, 36
Observations following pituitary suppression by heavy-particle therapy, 277–289
Observations on the pathogenesis of diabetic retinopathy, 47–53
Occlusion
  arterial, 639
    photocoagulation, after, 556
  central vein, 634
  lumina of terminal arterioles, 61
  retinal vein and neovascularization, 555
  vascular photocoagulation ascribed to, 611
Ocular architecture intricacies complicating retinopathy, 222
Ocular aspects of pituitary ablation, discussions of, 380–393
  summary of papers on, 375–379
Ocular evaluation prior to ruby laser photocoagulation, 441
Ocular hypotony, 651, 658
Ocular intravascular pressure, avoidance of stress causing, 175
Oculomotor nerve
  distance to pituitary varies, 369
  necrosis not seen in 2000 implantations of yttrium-90, 423
Ocular responses after cryohypophysectomy, 348–350
Ocular results and pituitary function correlation, 220
Ocular tension, 253
O'Hare Classification, XIX, 7, 22, 23, 24, 25, 28, 37, 81, 83, 98, 204, 215, 216, 224, 241, 254, 255, 259, 261, 267, 281, 286, 287, 314, 315, 316, 332, 348, 353, 375, 376, 377, 444, 447, 448, 487, 499, 507, 508, 509, 515, 541, 542, 556, 559, 560, 565, 596, 618, 620, 653, 691, 701, 702, 704, 707, 710, 780
  Hammersmith grading system compared with, 29
  incidence of components tabulated, 348
  misinterpreted?, 704
  note on, XXI–XXIV
  "should be a thing of the past," 31
  tabulated, 84
  testing of, 7
O'Hare meeting, the, 523

Okun, Edward, VI, XI, XII, XIII, XIV, XIX, XXI, 7, 22, 23, 25, 37, 93, 101, 386, 462, 468, 475, 482, 484, 487, 488, 494, 506, 514, 523–535, 543, 545, 553, 568, 592, 601, 609, 613, 615, 617, 619, 623–629, 631, 632, 635, 637, 640, 643, 646, 647, 650, 652, 692, 696, 700, 703, 704, 714, 720–721, (Data) 787–816
Olivecrona, H., 310, 331, 341, 395, 417, 722, 728
Oosterhuis, J. A., 169
Operative procedure in photocoagulation, 470–471
Ophthalmodynamometer ophthalmic artery pressure measuring by, 657
Ophthalmologic examinations following hypophyseal stalk section, 216
Ophthalmologic grading and metabolic followup after proton beam pituitary suppression, 252
Ophthalmologic reevaluation after pituitary ablation, 207
Ophthalmologic results
  endocrine factors affecting, 250
  following radiofrequency coagulation, 209
  ophthalmologic factors affecting, 250
Ophthalmologic evaluation, lack of expert, 721
  patients for cryosurgery, of, 342–343
Ophthalmological observations following heavy-particle radiation therapy, 277–289
Ophthalmological observations following radiation therapy, 277–289
Ophthalmologists, 147, 150, 277, 564
Ophthalmology, XIX
  indirect binocular, 47
  pituitary suppression by proton beam, in, 256
  stereoscopic fundus photography, 47
Ophthalmopathologic Laboratory, Copenhagen, Denmark, 673
Ophthalmoscopy
  classification, importance in, 8
  indirect binocular, 9, 34
Ophthalmoscope in classification, 35, 36
  photography, combined with, 11
Ophthalmoscope—Continued
  ophthalmoscopic classification of patients—form for recording, 17
Optic chiasm variation a surgical disadvantage in pituitary ablation, 196
Optic nerve
  elevation of during stalk section, 355
  fibers originating in the hypothalamus, 235
Optics Technology laser, 523, 637
Orientation of patient before ruby laser photocoagulation, 442
Orthostatic hypotension following hypophysectomy, 309
Oscar Johnston Institute, 523
Oscillations in ERG measurements, 683
Oxford (England) blindness study, 44

P

Packman, Robert, XVII, 143, 412
Palliative procedures—photocoagulation and pituitary ablation are, 422, 557
Palo Alto Medical Clinic, Palo Alto, California, 603
Paloyan, E., 373
Palsies
  cranial nerve, 195
  extraocular, 421
  yttrium-90 implants, following, 341
Pancreatic failure and vascular disease, 116
Panhypopituitarism, 371, 415
Panisset, Alain, IX, XIII, 235–247, 748–750
Papillomacular area, abnormalities in the, 595
Parameters of classification, photographic standards for, 22
Paresis following coagulation-type pituitary ablation, 206
PAS staining, 673
Pathogenesis of diabetes mellitus, 465–466
Pathogenesis of diabetic retinopathy, clinical observations on, 47–53
Pathologic patterns, detailed study by high-power magnification of photographs, 545

Pathological arterioles
see also Arterioles, pathological
Pathology lying outside disk-macula area, 638
Pathophysiological investigation of diabetic retinopathy, a, 235–247
Patients
categories in laser photocoagulation series, 603, 604
classification and speed of deterioration of, 36
classification of, 36
details of those receiving pituitary ablation by radiofrequency coagulation, 204
evaluation for cryosurgery, 342–346
rejection for stalk section based on test findings, 362
selection
heavy-particle radiation therapy, for, 278
Johns Hopkins Hospital, at 564–565
long-term visual retention, and, 698
morbidity, and, 418
mortality, and, 418
photocoagulation therapy, for, 507
tendencies during acute illness, 180
unfit for surgery-proton beam used for, 249–276
with proliferative retinopathy 10 to 14 years after diagnosis of diabetes, 142, 143
Patnaik, B. K., 354, 728
Paton, David, 564
Patz, Arnall, VII, VIII, XVII, 35, 87–91, 97–98, 219, 225, 474, 475, 477, 568
Pazianos, A. G., IX, XIII, 227–234, 729, 743–747
PBI studies, 281
PBI test following radiation therapy, 283, 284, 285
PBI test variations, 296
Peabody, R., 671
Pearson, Olof H. IX, XIII, XVII, 233, 234; 289, 311, 331–339, 351, 353, 404, 413, 415, 416, 418, 494, 696, 700, 103, 723, 726, 729 (Data) 762–767
Pei Fei Lee, 253, 275, 276
Plasma and 17-hydroxycorticosteroids measurement, 334
Peretz, Walter L., IX, XIII, XVII, 26, 29, 36, 392, 393, 729 (Data) 743–747
Pericytes ("mural cells"), 48
Peripheral vision reduction following photocoagulation, 469
Personal impressions of symposium (Davis), 718–719
Peter Bent Brigham Hospital, Boston, Mass., 172
Phenobarbital, 230
Phlebopathy and edema, 306
Photocoagulation, XIX, XXI, 8, 52, 81, 88, 94, 216–217, 437–653, 479–484, 507–514, 692, 720–721, (Data) 782–786
advanced cases, didn't work on, 630
age distribution of patients undergoing, 539
aims of treatment, 469, 528
anesthesia, bleeding following, 599
anesthesia, local, performed under, 495, 556
anesthesia of choice in, 781
aneurysms, of, illustrated, 642
areas of, illustrated, 491
arterial caliber, changing, 720
arteries, of, 524
"at best a stopgap measure", 553
before and after illustrations, 529–534
benefit suggested but not proved, 710
benefits of, 490
blood column revealed during, 61
blood in vitreous and result of treatment, 512
blood in vitreous following classifications, 511–512
blood vessels decrease in size following, 640
burn to area of neovascularization right near disk, illustrated, 493
burn to paramacular area, 491
case selection for, 507, 508
cataracts, and, 632
choice of treatment considerations, 515
clinical material—60-eyes series, 479
coagulation intensity, 570

Photocoagulation—Continued
Comberg's xenon-arc instrument, 552
comparable to x-ray treatment for cancer, 728
complications of, 610–611
arterial occlusion, 482
extension of retinoschisis, 482
hemorrhage during operation, 483
how frequent are they?, 617
infrequent, are, 473–474
listed, 518, 629
major, 720
retinal detachment, 482
conditions for, ideal, 630
continuation and followup studies, 523–535
data on, 787–816
contraindications, 481
connective tissue bands, 481
new vessels near macula, 481
new vessels on the disk, 481
control series answers required, 614–615
Copenhagen series
complications in, 505
conclusion, 505–506
grouping details, 495–499
results tabulated, 501–505
retinal detachment in, 505
correlation of results with severity of proliferative diabetic retinopathy, 511
cryohypophysectomy, and complementary therapies at UCLA, 648
cryohypophysectomy, as an adjunct to, 537–544
decision to proceed with based on examination findings, 470
delimiting barrier of, diabetic retinal detachment in, illustrated, 549
diabetic retinopathy for, 465–477, 507–514
diagram of ruby laser burns, 439
direct hit on vein causing occlusion, 640
disk and retina 2 years after treatment, illustrated, 625
discussion of 283-patient series, 528–534
Photocoagulation—Continued
discussion of visual and anatomic results of, 612–622
dosage in Dobree's series, 480
early stages, beneficial in the, 577
early treatment with recommended, 582
edema, retinal, and, 577, 608
effectiveness not yet proven, V
effects of, the, 516–517
effects of treatment, 471–473
effects on new vessels, 516–517
effects on subsequent retinal detachment, 517
8 years' experience, Thornfeldt's, 555
factors, other, and—not related to success of treatment, 512
failures of treatment, causes of visual loss in, 513
favorable results of, 495
fibrosis, preretinal, and, 618
fibrous proliferation its effect on, 518
field defects associated with burns, 491
55-patient study analysis, 475
filter used in, 516–517
first used in 1955–59, 569
5-year prognosis of Beetham, and the, 622
fluorescein pooling and xenon-arc energy absorption, 647
fluorescein studies following, 440
followup by photography, longtime, 577
followup timing after, 647
fundus changes, and, 720
fundus, whole—coagulated in one session, 570
hazards minimal in, 593
hemorrhages new, and, 572
how often should treatment be given?, 647
hypophysectomy, after, 648
hypophysectomy, and, 615
in some areas affecting retina in other areas, 643
increasing, use of is, 611
indications and contraindications for, 631

Photocoagulation—Continued
indications for, 468
tabulated, 508
initial examination in University of British Columbia series, 487
intensity and number of applications tabulated, 511
Johns Hopkins Hospital at the, 565
laser and xenon-arc treatments, 636, 637
laser, by, 603–605
laser, Optics Technology type in, 523
lasers, red, 639
laser type, 564
differences in use of, 638
patient categories in, 603
possible future treatment, 604–605
scotoma following, 646
limited application, has, 507
lipid reabsorbed after, 641, 642, 643
lessened visual loss incidence, 706
macula burned by, 618
maintenance of vision sole criterion of treatment, 515
maximum number of lesions treated at sitting, 624
mechanisms of, 52
method in 232-patient series, 593–595
method of Retina Service of University of British Columbia, 486
microaneurysms, and, 608
multiple treatments necessary, 510
neovascularization, flat, and, 486
new fans and new vessels—management of, 639
number of treatments per eye tabulated, 510
objectives of, 607–608
1,500 eyes, experience on, represented at symposium, 623
1,800 eye—results in, 608
127-case study—results in, 570, 577–578
optimum time for, 513, 530
patient preparation for, 538
patient selection in Mortimer's series, 515
Photocoagulation—Continued
patients, criteria for selection of, 175–178
photocoagulator settings, 471
pituitary ablation, 648
after, 188, 508
no consensus arrived at, 718
pituitary ablation, versus, 649
preoperative and postoperative findings in patients, 541, 542
procedure detailed, 470–471
proliferative diabetic retinopathy, for, 485, 494
data on, 778–779
preliminary report, a, 495–506
prognosis, and, 469
"progressive" or "static" used in case assessment following, 510, 512
random type, 546
rationale, 479, 545–553, 616–617
data on, 820–827
items listed, 546
laser type treatment of, 603
necessity for, 545
red-blood-cell counts in vitreous following, 560
repeat operations, 481–482
repeated treatments, criteria for, 520, 521
results, 524–528, 569–592
correlated with disease severity, 511
Dobree's 42-eye series, in, 483
46 eyes, of, 539–541
illustrated, 571
Mortimer's series, in, 515–518
prognosis, and, 474–476
32-patient series, in, 539
University of British Columbia series, 489
retinal detachment, and, 528
retinal detachment from, 648
retinal detachment remedy, as a, 488
retinal detachment, subsequent, its effect on, 517
retinitis proliferans, for, 547, 555–562
retinal traction and detachment increased by, 542
retinal vascular disease control, for, 465

Photocoagulation—Continued
review of 232 patients treated by, 593–601
role of, the
continuation and followup studies, 523–535
nonproliferative retinopathy with impaired vision in—documentation needed on, 609
ruby laser type, 437–463
advantages of less complications, 460
clinical impression following, 452
clinical material and methods, 441–446
complications in clinical groups of retinopathy, 446
control eyes, and, 619
correlation of medical data on groups of patients, 446
"disturbing questions, two", 461
equipment, 441
examinations eight months following treatment illustrated, 457
fluorescein angiographic studies following, 444
fluorescein evaluation before treatment, tabulated, 449
fluorescein photography following, 443
fluorescein studies in treated and untreated eyes, tabulated, 450
followup examinations detailed, 444
group classification illustration before and after treatment, 456
group classification of worsening prognostic signs, 440
groups treated, 445
instructions to patient after treatment, 443
insulin reactions, and, 451
lesions, the number of, 443
list of, 637
medical evaluation of patients before, 445
monkey experiments comment-on and summary of, 668–671
monkeys, used in, 665–671
nature of ruby light, the, 460
ocular evaluation, preoperative, 441
Photocoagulation—Continued
ruby laser type—continued
O'Hare Classification modifications in postoperative grading, 444
orientation of patient before treatment, 442
preliminary report, a, 437–653
preoperative findings, 441, 442
procedure in, 442–443
results and effects on early neovascularization of disk, 448–450
results and effects on neovascularization at retinal level, 446–448
results, evaluation of, 444
results of treatment, 446–453
retinalchoroidal metabolic ballance, and the, 462
statistical analyses of response by patient-groups, 453
"the most promising," 439
value of, the, 714
significant data on treatment by, 475
64-patient series reported by Mortimer, 515–521
statistical analysis study in 127-case report, 577
statistical followup information required on, 650
still experimental, 119
subhyaloid hemorrhage, and, 550
success or failure of treatments difficult to determine, 510
summary of treatment techniques papers, 623–629
summary of 283-patient series, 534–535
symposium has 16 papers on, 607
tabulated results of, 564
technique, 480
Dobree's 480–481
therapy, initial, 523–524
treatment, 538
method of, 569–570
Mortimer's 64-patient series, 519–521
rationale, 607–608
techniques of discussion of, 630–653

Photocoagulation—Continued
treatment—continued
techniques—summary of papers on, 623–629
29-patient series of University British Columbia—summary of, 490–494
292-patient series of Thornfeldt, 555
comment on, 600
complications in, 599–600
results in, 595–599
University of British Columbia series—results in, 487–488
untreated retina, its effect on, 518
uses tabulated, 607–608
vascular lesions, treatment of, 630
vision loss, peripheral, after treatment, 469
vision of treated eye at time of, tabulated, 510
vision of untreated eye at time of, tabulated, 510
visual acuity before and after, 527, 540, 571, 572, 573, 574, 575, 693
visual fields assessment in patient selection for, 507
visual fields before and after, 576
visual fields defect produced by, 492
visual field defect from, illustrated, 493
visual and anatomic results, summary of, 607–611
visual results comparison, 702
visual results evaluated, 476
vitreous contraction, its effect on, 517
vitreous slit-lamp studies necessary preoperatively and post operatively, 562
vitreous studies in, 559–562
vitreoretinal adhesions, may cause, 513
vitreoretinal traction and, 512
what stimulated this approach?, 612
when to start treatment?, 630
Wilmer Institute, at the, tabulation, 566
xenon arc type—complications, occasional, 637
xenon "green" photocoagulation, 461
xenon light, by, 438
Photocoagulation—Continued
xenon type, 627
Zeiss photocoagulator in, 480, 507
Photography
see also Fundus Photography
classification by, 22
classification of patients by—form for recording, 19
color photographic standards, 11
degrees of fundus in, 35
discussion on number of photographs, 24, 25
discussion on reading eye photographs, 130
8-year photographic survey of lesion evolution, 55–64
error of reproducibility, 130
fields for standard use, 18
fields recorded by Zeiss fundus camera, 10
fluorescein photograph before and after pituitary ablation, 153–169
form for recording photographic evaluation of patient, 19
fundus type, 47
grading of individual photographs, 4, 34
Hammersmith grading system, used in, 6
individual parameters and, 4–5
montage effect, 24
nine fields should be photographed, 25
not assessable, 322
ophthalmoscopy, combined, with, 11
photographic fields illustrated, 10
sequence of, 27
standard, 3–4, 6
standards for all parameters of classification, 22
diabetically diseased eyes, for, 725
retinal, 65
retinopathy, a method of grading, 34
technical quality important in grading assessments, 6
usefulness of, retinopathy and, 35
vitreous hemorrhage grading, and 20
Physiologists, 150
Pigment clumping, 455

Pigment, epithelium and choroidal vessels diabetic and normal, 676
Pigmentation, macular, illustrated, 62
Pitressin, 201, 230, 240, 273, 295, 335, 421, 423, 717
Pituitary
anatomical variations noted, 430
anterior, infarction of, 235
appearances of lobes of, 237, 238, 239
circulation studies, 195
destruction for angiopathic diabetic retinopathy, 203
eight methods of destroying the, 422
enucleation of, 243
enucleation of anterior lobe, 237
fossa entrance adequate in nine of ten patients, 196
function and ocular results correlation, 220–221
function data summarized, 269, 270
function measurements, 400
functions of, early confusion about the, 147
histological examination of removed gland, 263
hormones, direct assay unavailable, 242
hypofunction — techniques for obtaining, summary of, 415
implantation, 120
infarction of, spontaneous, 277
inconsistent state of infarction, 433
insufficiency, 217
determination of degree of, 263
lobes, anterior and posterior, locations described, 236
particularly adaptable to freezing procedure, 363
physiology and pathology of the, 147
posterior powder, insufflation of, 230
preservation of posterior lobe, of, 429
regeneration following surgery, 433
stalk section results, 489
subnasal approach to, illustrated, 237
surgical approach to the, illustrated, 237
Pituitary—Continued
width of, the—anatomical studies, in, 366
Pituitary ablation, V, XXI, XIX, 8, 65, 81, 120, 227–234, 331–339, (Data) 743–747
see also Hypophyseal stalk section
see also Hypophysectomy
see also Pituitary suppression
see also Radiofrequency pituitary coagulation
adjustment of patient, and, 177
adrenal function, and, 182
advantages of adequate surgical exposure in, 431
adverse effects of, possible, 174
age limitation, 228
almost sightless patient, and the, 228
amputations and vascular disease, and, 233
anatomical anomalies of pituitary, and, 239
anatomical appearance during surgery illustrated, 197
anatomical variations in surgical exposure, 196
angiopathy and hemorrhage cessation following, 185
angiopathy responds to, 313
animal experiments in year 1930, 291
anterior pituitary ablation, selective, 235–247
approaches, ablative, 194
bacitracin solution used in surgery, 200
benefit suggested but not proved, 710
blindness, and, 178
blood sugar control following, 408
capillary closure, not causing, 159
cardiovascular function in patients considered for, 229
cerebral damage during, 195
cerebral edema following surgery, 201
changes following, 150
clinical criteria for operability, 227
clinical usefulness of, 213
"complete," 93
completeness, assessment of, 230
complications, postoperative, 188

Pituitary ablation—Continued
conclusions of summary of papers on, 379
contraindications to, 177, 313
convulsive episodes following surgery, 200
cranial approach, the, 194
criteria for patients' acceptance for hypophysectomy, tabulated, 292
criteria formulation for patients undergoing, 230
cryodestruction technique, 210
cryohypophysectomy
an effective method of, 351
diabetic retinopathy, and, 341–354
cryosurgery, by, 342
data on, 762–767
death following, 230
decade of neurological experience with diabetic patients, 193
degree of following yttrium-90 implant, 321–327
diabetes insipidus following, 206
diabetic retinopathy and—historical summary, an, 147–151
endocrinological parameters in 30 patient series, 296
endocrinologic status evaluation, 173
evaluation of widespread, 341
experiment involving 30 patients, conclusions and summary, 309
eyes at risk, tabulated, 181
eye evaluation following, 174
features responding to summarized, 377
fibrous proliferation following, 187
fluorescein photography following, 153–169
fluorescein photography shows results, 159
fundus diagrams in, 229
gland, clear exposure of the, 196
gonadal function assessments following, 333–334
grade of related to retinopathy response, 324, 327
growth hormone, and, 182, 232, 542
Hammersmith grading system, and the, 3
head rotation in surgery illustrated, 199
Pituitary ablation—Continued
heat method of tissue destruction, 210
hemorrhage following, eye, 185
hormonal management following, 229
hormone replacement following, 230
hypophyseal stalk section, 213–225
treatment for diabetic retinopathy, as—ocular aspects, 313–316
hypophysectomy and diabetic angiopathy, 291
hypophysectomy for diabetic angiopathy, a controlled clinical trial, 291–311
hypophysectomy, optimum time for operation, 292
hypophysectomy, surgical observations on, 193–202
hypophysectomy, transsphenoidal—results tabulated in 30-patient series, 295, 296
hypopituitarism, degree of following, 185
hypopituitarism produced by, 715
improvement, following, 189, 232
improvement following—but no return to normality, 381
inadequate, 172, 193
inconsistency of results, 515
instrumentation from below, 194
intelligence of patient, and, 229
investigation of completeness of, 244
irradiation following, 173
labile patients and testing for hypoglycemia, 402
lobes of pituitary, different appearances of, 237, 238, 239
long-term results presented, 331
low stalk section described, 239
management, 178–180
measure of desperation, considered as a, 224
measurement of, 716
medical aspects of discussion of, 400–413
medical aspects of summary of papers on, 395–399
medical evaluation, followup, 208

Pituitary ablation—Continued
medical evaluation of candidates for, 203
meningitis following, 231
menses, and, 182
metabolic changes following, 176
methods of, 227
methods of assessments of, 242–246
methods of performing, 227
methods of, summarized, 341, 342
microsurgical technique, 236
microsurgery in
illustrated, 238
postoperative management, 239–240
preoperative management, 239–240
minimal, 173
miscellaneous methods of, 395
mortality following, 189
mortality, surgical, elimination of, 227
motivation for must be assessed, 178
nephropathy, effect on, 427
New York Hospital—Cornell Medical Center, at, 227
ocular aspects of,
discussion of, 380–393
summary of papers, 375–379
operations tabulated, 183
operative procedures and substitution therapy, 294
ophthalmic criteria for patient selection, 375
ophthalmological evaluations before and after treatment, 333
palliative procedure, a, 422
partial, a poor contraceptive, 407
patients
over age 40, and, 228
do not remember operation, 428
not suitable for, 313
patient population in coagulation series illustrated, 205
selection, 227, 230, 231, 417, 418
water intake control following, 179, 405
pituitary infarction, and a recorded spontaneous, 341
pituitary stalk section, 331
Pituitary ablation—Continued
pituitary suppression by proton beam, 249–276
pituitary suppression by radiation —observations following, 277–289
pituitary suppression rating, 182
posterior lobe preservation, 429
postoperative complications, tabulated, 180
postoperative endocrine appraisal, 204
postoperative evaluation, 173
postoperative fluid problems, 421
postoperative management following surgery, 201
postoperative oral fluid intake, 207
postural hypotension following, 179
preoperative complications tabulated, 181
preoperative management of coagulation patients, 205
preoperative medical evaluation, 203
procedures for attaining moderate pituitary insufficiency, 173
procedures in 895 patients · tabulated, 395
psychiatric evaluation, and, 175
psychological disturbances following, 406
photocoagulation and, 648
no consensus arrived at, 718
palliative procedures, are, 557
photocoagulation, by, 635
photocoagulation
compared with, 488, 489
following, 188, 231, 508, 614
versus, 649
radiofrequency coagulation, 203–212, 342, 365–373, 416, 420
mortality, 208
patients chosen for, 204
results, 208–209
removal of pituitary in one piece, 332
renal complication following, 228
renal function and, 204
renal function, and adequate, 228
renal function reduced by, 717
report on 52 patients, 331–339
results, 489
30-patient series, 230–232

Pituitary ablation—Continued
78-patient study, 230–232
tabulated, 180
retinal lesions, effect on, 233
retinitis proliferans absence, and, 228
retinopathy features responding to, 375
risks associated with, 292
salt intake following, 179
simple low section, 172
specimen of enucleation of pituitary, illustrated, 432
sphenoid sinus opened in, 196
spinal drainage mandatory in surgery for, 198
spontaneous remission mimicking, 189
stalk section, 355–364
stalk-section series and radiofrequency coagulation series compared, 204
stereotaxic method defended, 433
still experimental, 119
suppression, and—results compared, 278
surgeon's skill more important than method, 194
surgical, 171–191
findings following, 171
mortality rate, 172
operative procedures, 172–173, 198–200, 229–230
summary of results in 87 patients, 190
surgical and implantation types, statistics tabulated, 231
surgical procedure and management, 229–230
surgical aspects of
discussion of, 422–434
summary of, 415–421
survivors' status, 190
systemic effect on patient, has a, 649
techniques for hypophysectomy, 331–332
techniques for, summary of, 415
thermal change, by, 150
30-patient series summarized, 246
three techniques employed in 52-patient study, 331–339
Pituitary ablation—Continued
thyroid function, and, 182
thyroid function tests after, 333
timing, the importance of, 193
transnasal approach for implantation for, 230
transsphenoidal hypophysectomy complications and deaths, 295
transsphenoidal operation, 194
transsphenoidal stereotaxic technique in, 203
28-year-old male, in—fluorescein photography following, 161
24-year-old female, in a—illustrated, 163
unreliability of patients assessment of, and, 333
vascular complication following, 227
vascular lesions on, 233
vascular parameters in 30-patient series, 296
vasopressin administered postoperatively, 207
visceral vascular changes, inducing, 233
visual acuity, and, 693
visual course, surviving patients', 185
visual impairment, progressive, and, 228
visual results
comparisons, 701–710
following, 375
summarized, 184, 377–378
visual status following, 186, 187
vitreous clearing an objective sign, 652
what degree is necessary? 399
yttrium-90 in, 227, 317–329
degree achieved by, 320
Pituitary suppression
see also Pituitary ablation
age of patient at onset of retinopathy and prognosis, 285
arginine studies in, 281
arginine tests following, charted, 284
Bragg peake of the proton beam in, 249–276
criteria for, 255
data on punch cards for IBM sorter, 256
failure of previous attempt at, 253

Pituitary suppression—Continued
growth hormone assay in, 281
Harvard Cyclotron used in, 250
"how much is required?", 278
irradiation dosages received by pituitary and adjoining structures illustrated, 251
irradiation-treated patients, 37, results tabulated, 286
isodose curve in proton beam irradiation, 251
metabolic changes, and, 282–285
metabolic changes following irradiation, 284, 285
no mortality in 171 procedures, 249
162 patients studied, 279
ophthalmology in, 256
patient selection for proton beam procedure, 260
patients and procedures defined, 250–256
patients', hopeless, exclusion of, 260
PBI studies in, 281
preexamination procedures, 253
prognosis for success lessened for, 255
proton beam alignment in, 250
proton beam, by
conclusions, 275
discussion, 273–274
dosage in, 251
economic procedure, an, 274
endorsed by medical community, 273
hypophysectomy contraindicated, 255
life table, 271
morbidity, 272
mortality in, 271
ophthalmology, and, 256
patient's general condition, and the, 255
patients receiving previous treatment, 252
proliferation, its effect on, 258
surgically "unfit" patients, in, 249–276
time of procedure, 252
radiation dosage in, 278
retinal evaluations in, 281
Pituitary suppression—Continued
survival following, 279–281
survival rates compared in different methods, 280
survival statistics, 279–281
unfitness for surgical procedure, and, 252
visual acuity ratio versus pituitary function (139 eyes), 271
Pituitary target organ function tests, 174
Plasma
escape of, 58
lipids and lipid intake, 115
proteins
yttrium-90 implant, following, 320
Pneumonia, 271
Polaroid film in proton beam procedure, 251
Poll of audience regarding hypothetical retinopathy situation, 652
Polydipsia, 179
Polyuria, 179
Popkin, A. B., 688
Post-mortem systemic findings after hypophysectomy, 722, 726
Postoperative complications following pituitary ablation, 188
Postoperative evaluation following pituitary ablation, 173–174
Postoperative management of coagulation patients, 206–207
Postural hypotension, 188
following pituitary ablation, 179
Potency following pituitary ablation, 407
Potentia, male, retained after pituitary ablation, 207
Powell, E. D. V., 212, 225, 399, 729
Poulsen, J. E., 46, 91, 100, 235, 236, 247, 288, 291, 310, 331, 353, 339, 477, 564, 568, 659, 663, 681, 722, 728
Poulsen's observation on the regression of retinopathy, 149
Potassium, total exchangeable, 229, 232
Poskanzer, David C., 275
Precorneal contact lenses in classification, 36
Prednisone, 294, 320
Pregnancy, diabetic, 142
cotton-wool exudates in, 101
hypophysectomy, after, 726

Preliminary Report on ruby laser photocoagulation, 437–653
Preoperative management of coagulation patients, 205
Preretinal fibrous tissue, 5
Presbyterian Hospital of Pacific Medical Center, San Francisco, Calif., 465
Pressure
  arteriolar versus venular, 662
  intra-arterial-lower, natural, 661
  intra-arteriolar measurements of, 662
  intraocular, 661
  intraocular and intraretinal, 651
  ratios in diabetic retinopathy, 657–663
  vascular, 661
  vascular pressure ratio concept, the, 663
  venular versus arteriolar, 662
Preston, William M., 249, 275
"Preventive" photocoagulation, 719
Prichard, M. M., 195, 202
Primary changes in PDR defined, 55
Primary lesions, observations on, 56–63
Primotestone-depot, 320
Prognosis
  classification, and, 32
  ERG an aid in, 688
  retinopathy, age of patient at onset of, and, 285
  ruby laser photocoagulation group classifications listed, 440
  statistical, 98
  visual
    diabetic retinopathy, in, 41–46
    15 diabetics, tabulated in, 42
    natural history, and, 39–103
  vitreous hemorrhage, after, 43
Progression of retinopathy—great variations in, 713
Proliferations, fibrous appearances of, 50
  effect of proton beam on pituitary suppression, 258
  naked and fibrous vessels compared, 30
  plane of, 12, 16, 35
    evaluation of, 19
Proliferative diabetic—Continued
  preoperative grades, 255
  preoperative, vision outcome and, 258
  ratio of, 254
  proliferation-angiopathy correlation, degree of, 258, 259
  proliferative changes, XXII
Proliferative diabetic retinopathy
  an enigmatic process, 485
  anoxic phenomenon, an, 617
  arrested case illustrated, 165
  changes in, primary and secondary, 55–56
  comparison of visual results, 701–710
  early-stage treatment beneficial, 577
  8-year study-clinical material in, 55
  ERG readings in, 684
  eyes with initial visual acuity of 20/40 or better, followed for 1 year or more, 95
  fluorescein findings in, 157
  fluorescein photography particularly useful in, 167
  illustrated, 590, 591
  late changes in macular area, illustrated, 62
  lesions appear and disappear during, 34
  lesion sequence in, 55
  nonproliferative to be considered separately, and, 608
  photocoagulation for, 479–484
    followup studies, 523–535
    preliminary report, a, 495–506
    results, 476
  pituitary ablation, treated by fluorescein photography in, 153–169
  primary changes in stages of, 56
  progression following photocoagulation, 489
  progression in eyes treated by photocoagulation, 526
  rarely develops after photocoagulation, 578
  secondary changes in 112 eyes tabulated, 58
  secondary changes in, tabulated, 57
  severe, 90
  severity in 100 eyes series tabulated, 509

Proliferative diabetic retinopathy—Continued
stalk section, and, 314
statistics, question on, 99
summary of 283-patient series, 534–535
treatment, effective, and, 98
uniocularly treated by photocoagulation, 527
visual prognosis, and, 42
visual retention, and 705, 708, 709
vitreous hemorrhage worse than, 99
Proliferative lesions, components of, 14
Proliferative lesions difficult to classify, 14
Proparacaine hydrochloride, 470
Proton beam pituitary suppression, 249–276, 425, 692
Bragg Peak, 249–276
data on, 751–761
see also Pituitary suppression
Proton beam radiation in pituitary ablation, 195
Protein-bound iodine, 204
see also PBI
response of, 269
test, 174
Proteinuria, 445
persistent, 43
Prout, Thaddeus E., 564
Psychiatric assessment of patients, 406
Psychiatric evaluation prior to pituitary ablation, 175
Psychiatrist a "silent partner," in patient selection, 427
Psychiatrist, the, 538
Psychic factors in diabetic retinopathy, 116
Pulmonary embolism, death from, 418, 419
Pulmonary embolus, 189, 359, 360
Pulmonary tuberculosis and diabetes, 291
Pupillary dilatation important in photocoagulation, 471
Pyelonephritis, 228

Q

Quiescent stage of diabetic retinopathy, 100

R

Ray, Bronson, XIII, XVII, IX, 169, 195, 199, 202, 227–234, 276, 339, 353, 376, 378, 415, 416, 417, 418, 419, 420, 421, 422–434, 494, 644, 722, 727, 728, 729 (Data), 743–747
Rabinowitch, I. M., 129, 131, 289
Rabkin, M. T., 729
Radcliffe Infirmary, Oxford, England, 107, 129
Radiation
see also Irradiation
see also Pituitary suppression
hypopituitarism, to produce, 149
implant type, 564
necrosis of carotid artery, 336
transcutaneous, 341, 564
Radioactive gold pituitary implantation, 149, 395
Radioactive iodine uptake, 174, 204
Radioactive yttrium-90
see Yttrium-90 implantations
Radiofrequency heat coagulation, 342
Radiofrequency pituitary ablation
complications following, 371
discussion on, 372
easily tolerated procedure, an, 373
landmarks, anatomical, missing, 369
meningitis following, 371
operation, duration of, 371
results of 65-patient series, 371
rhinorrhea following, 371, 372
stereotaxic technique, 370–371
teleradiographs in, 370
Radiofrequency pituitary coagulation for angiopathic diabetic retinopathy, 203–212
data on, 739–742
discussion on, 210–211
Radiofrequency thermal hypophysectomy, 395
Radioimmunoassay measurements before and following pituitary ablation, 334
Radiosurgeons, 277
Ramos, E., 191
Rand, Robert W., IX, XI, XIII, XVII, 150, 202 341, 353, 354, 373, 375, 378, 418, 419, 427, 429, 431, 434, 537, 544, 609, 696, (Data) 768–772, 817–819
Rappaport, F., 310
Rasmussen, Jens H., IX, 291–311, 373

333-611 O - 69 - 59

Rat—diabetes experiments on findings in, 143
Rationale for photocoagulation, 510, 545, 553, 607–608, 616–617
Red-blood-cells counted in vitreous, 559–560
Rees, Searle B., VII, 153–169, 171–191, 202, 247, 275, 276, 462, 707, 715
Regimens, therapeutic, XXI
  multitude of, a, 22
Regression expected in a 62-year-old photocoagulation patient, 586
Regression of diabetic retinopathy, 60–61
Remissions, spontaneous, V
  see also Spontaneous remission
  diabetic retinopathy, of, 518
Remission of diabetic retinopathy following photocoagulation, 593
Remission of diabetic retinopathy a late feature of natural progress of disease, 485
Renewed pituitary activity following ablation, 393
Renal autopsies, 232
Renal biopsies, 229, 232
  hypophysectomy, before and after, 352
  patient evaluation, in, 177
  preoperative, 224
Renal deaths, 391
Renal disease, 427
  diabetic, 221
  may improve after pituitary ablation, 722
Renal failure, 281
Renal function
  complication of pituitary ablation, a, 188
  decrease after pituitary ablation, 177
  diabetes mellitus, impaired by, 227
  evaluation findings summarized, 231
  investigation of following pituitary ablation, 229
  pituitary ablation, and, 204
  reduced by pituitary ablation, 717
  selection of patients for pituitary ablation, and the, 228
  surgery, worse following, 223
  values detailed, 228
Renal impairment, severe hypophysectomy and, 332
Renal pathology and hypophyseal stalk section results correlation, 221
Renal plasma flow evaluation, 231
Rentiers, P. Kenneth, X, XIII, 485–494, (Data) 778–779
Results of photocoagulation
  diabetic retinopathy, in, 569–592
  Mortimer's 64-patient series in, 515–518
  32-patient series, in, 539–541
Rete mirabilis, 591
Retention of vision, likelihood of, 693
Retina
  abrupt downhill course in patient selection, and, 418
  attached, proliferations, and, 16
  changing pigmentary character of, observation of, 458
  characterization of, XXI, XXIII, XXIV
  decreasing metabolic requirements of photocoagulation, by, 639
  detachment of
    see Retinal detachment
  diagrams of the, 306
  normal, illustrated, 675
  pathological changes in, 55
  proliferation, and, 16
  reduction of metabolic demand of the, 631
  traction on the, 255
  transit times in, 380
  visible, XXII
Retina Service of the University of British Columbia, 486
Retinal arterial tension, 659
Retinal arteriolar hypotension, 659–660
Retinal changes following hypophysectomy, tabulated, 306
Retinal circulation integrity should not be disturbed by photocoagulation, 481
Retinal detachment, 57, 262, 264, 265, 314, 315, 481, 482, 505, 518, 565, 632
  cryotherapy for, 635
  delimiting barrier of photocoagulation in, 549
  diathermy for, 619

Retinal detachment—Continued
exudative, 571
flat-holes and, 60
hypophyseal stalk section, 216
major complication in photocoagulation, a, 599
photocoagulation, after, 528
photocoagulation, ascribed to, 611
photocoagulation, from, 648
photocoagulation tried as a remedy for, 488
secondary, 513
spontaneous resettlement of, 594
subsequent to photocoagulation, 517
surgery, and, 60
surgical procedures used in, 633
traction type, 632
type differentiation, 635
Retinal deterioration when growth hormones persist, 401
Retinal diagrams, 253
Retinal disease, phases of
preproliferative, 466
proliferative, 466
Retinal drawings, 342
cryosurgery, and, 342
Retinal elevation, 30
Retinal evaluations, 281
Retinal hole treatment, 517
Retinal holes
postoperative results related to, 633
Retinal improvement, critical parameter for, 726
Retinal nutrition, reduced—diseases associated with, 473
Retinal peripheral areas deprived of nutrition, 546
Retinal separation following pituitary ablation, 187
Retinal separation, secondary, 437
Retinal vein distension, 437
Retinal vein occlusion, 57
Retinal vessel, small,
normal, 678
diabetic, 678, 679
Retinitis proliferans, 99, 171, 231, 232, 318, 327, 486, 490, 520, 547, 552, 565, 599, 603, 715
absence of, pituitary ablation and the, 228
diabetic control, and, 125
fibrous, 3, 4
Retinitis proliferans—Continued
footnote on, 171
improvement following pituitary ablation, 337
limitations of photocoagulation in treatment of, 557
new vessels distinctions, and, 4
not responsive to pituitary ablation, 321
photocoagulation for, 555–562, 608
prevention of, 546–547
Retinopathic process, the progress of, 249
Retinopathy, diabetic
see Diabetic retinopathy
Retinopathy, background, XXI
background type has better prognosis, 37
classification of Lee, 507
correlation between frequency of and glycosuria percentage, 112
flareup when thyroid replacement therapy given, 392
"florid", 319
frequency, glycosuria percentage, and the, 107
incapacitating, 292
location of, 35
metabolic control, and, 106–144
mixed, 508
nonangiopathic, 215
photographic grading, and, 34
proliferative, 30
rapid progression of, 37
retinopathy-metabolic control relationship, 132–144
sickle cell C type, 640
unstable diabetes and increasing severity of, 446
Retinoschisis, 57, 58, 60
localized, 59, 60
Retinovitreal adhesions, 607
Retinovitreal bands, formation of, 57, 59
"Retrovitreal" membrane, 467
Retraction, vitreous, 57
Revascularization of areas of capillary closure, 71
Review of selected aspects of diabetic retinopathy, 713–717

Rhinorrhea, 195
cerebrospinal fluid type, 208, 210, 341, 342, 419, 430, 434
occlusion of midline puncture, and, 372
radiofrequency ablation, after, 371, 372
yttrium-90, and, 365
nasal turbinate damage following, 345
Rilliett, B., 64
Roentgenograms, cryohypophysectomy, during, 345
Role of photocoagulation in therapy of proliferative diabetic retinopathy, 485–494
Root, H. F., 128, 191, 288, 494, 566
Rosenbaum, A. L., 477, 663
Roth, Nathan H., IX, XI, XIII, XVIII, 24, 33, 141, 341–354, 385, 386, 390, 416, 419, 428, 527–544, 609, 623, 640, 648, 692, 696, 700, 703 (Data), 768–772, 817–819
Royal Postgraduate Medical School, London, England, 65, 119, 318
Rubeosis iridis, 30, 57, 58, 63, 241, 253, 262, 264, 272, 306, 308, 315, 389, 390, 527, 599
photocoagulation, ascribed to, 64
photocoagulation has favorable effect on, 473
secondary, 387
Rubeosis retinae, 582
Ruby laser photocoagulation, 603–605
see also Photocoagulation
anesthesia, retrobulbar, not required in, 619, 623
Ruby laser
burns—placement diagrammatically illustrated, 439
coagulator versus Zeiss type, 556
emission primarily absorbed in the pigment epithelium, 458
effect on monkey retina, 665–671
light—the nature of, 460
photocoagulation equipment for, 441
Rucker, C. W., 276, 421, 353, 494, 719
Rutin, 81, 119
of no value, 119

S

Schalch, D. S., 289
Schaub, 247
Schepens, Charles L., 64, 149, 213–225, 494, 514, 562, 715, 717, 729
Schepens binocular indirect ophthaloscope, 253, 293
Schimek, Robert A., LVII, 392, 427, 616, 645
Schisis and retinal elevation, 16
Schlesinger, F. G., 119, 128, 129, 131
Schott, K., 592, 601
Sclera
diabetic, illustrated, 676
normal illustrated, 675
Scleral buckling, 634
operations, 81
procedures, 468, 541, 632
types of, listed, 633
Sclerosis
large vessel, 115
ruby laser photocoagulation, and, 450–451
Scotoma, 595
arcuate, 505
photocoagulation, ascribed to, 611
laser burn, following a, 646
Scotomata, localized, 491
Scott, A. W., 174
Scott, D. J., 168, 169, 353, 569, 729
Secondary changes in PDR defined, 56
Seeing Eye, Inc., 87
Sees, S. B., 191
Sella turcica
anatomical configuration of the, 243
anatomical study of, 365–370
hypophyseal fragments remaining in, 236
length correlated with distance between pituitary stalk and dorsum sella, 369
open surgery, in, 243
pituitary suppression procedures, in, 251
sealing after hypophysectomy, 239
surgical approach to, 236
Semilogarithmic plotting of disapperance of microaneurysms, 66
Senile macular degeneration, 631
Serial assessments, 6
Serum cholesterol test, 293

Serum electrolytes, 229
Serum creatinine, 229
Serum creatinine test, 293
Sexual drive and potency after hypophysectomy, 309
Sexual function, 407
  assessments, 716
  yttrium–90 implants, following, 320
Shealy, C. N., IX, XIII, 331–339
Sheehan, H. L., 663
Sheehan's syndrome, 149, 659, 661
Shikano, S. 169
Shimizu, K., 169
Shrinkage, vitreous, and pituitary suppression, 255
"Shunt hypothesis", Cogan's, 47, 48
"Shunt" vessels, 9
  intraretinal, illustrated, 15
  when do they develop? 102, 103
Silicone plug, 208, 210
Silicone rubber dumbbell, anterior sellar wall plugged with, 416
Simonsen, Svend E., XII, XVII, 46, 91, 100, 288, 410, 411, 477, 568, 681–689
Sjögren, Bjorn, 177, 191, 310
Skouby, A., 119, 128
Skovborg, F., 168
Slit-lamp biomicroscopy, 53
  classification, importance in, 8
  classification, in, 36
  contact-lens in vitreous classification, and, 561
  examination, 34
Snedecor, G. W., 562
Snellen chart for recording visual acuity, 121
Sodium excretion, urinary, 405
Sodium pentobarbital used in monkey experiments, 665
Soft exudates, 12, 22
  change in area following pituitary implant illustrated, 383
  commonness of, 48, 49
  illustrated, 381
  natural history of, long, 381
Soley, M. H., 310
Somatotropin, 223
Sorsby, A., 46
Spalter, Harold F., XI, XIII, XVII, 25, 31, 35, 617, 631, 635, 636, 639, 645, 647, (Data) 820–827
Speakman, J. S., 202
Spermatogenesis androgen therapy, and, 407
Sphenoid blocks, frozen, anatomical studies of, 236
Sphenoid sinus "concha" type, 430
Sphenoid sinus opened in pituitary ablation, 196
Spinal fluid leakage, 141
Spinal drainage mandatory in pituitary ablation surgery, 198
Spontaneous amelioration of retinopathy, 643
Spontaneous involutional changes in diabetic eyes, 530
Spontaneous regression, 569, 622
Spontaneous remissions of active advanced retinopathy are rare, 338
Spontaneous resettlement after retinal detachment, 594
Sprague, R. G., 494
Stalk section, 149, 313–316, 404, 564, 565, 692
  age and sex influence, 218–219
  blindness, impending and, 213
  cases of poor surgical risk, in, 331
  criteria for patient selection, 313
  demonstrable changes following, 222
  diabetes details in patients studied, 214
  diabetic retinopathy, in, 355–364
  evaluation and classification of results following, 215
  evaluation of response to, 314
  exacerbation of hemorrhagic events and neovascular activity, 221
  "failure" following, 216
  failure regression, causes of, 315
  fibrotic proliferation arrested by, 223
  heavy-particle radiation and surgical hypophysectomy survival rates compared, 280
  involutional phase, and the, 220
  management in hospital, 362–363
  mechanical barrier, in, 341
  mortality following, 217–218, 359–360
  ocular aspects of, 313–316

Stalk section—Continued
121-patient series, report on, 355–359
121-patient series summary and conclusions, 363
ophthalmologic examinations following, 216
patient rejection following tests, 362
patients over and under 40 years of age, compared following, 219
patients studied, details of, 213–216
pituitary function and ocular results correlation, 220–221
postoperative morbidity, 360–361
rapid effect of, 314
"regression" following, 216
renal pathology and, 221
results of tabulated, 315
retinopathy duration in patients studied, 214–215
retinopathy reversed following, 433
sex frequency disparity, patients', 214
sex of patients studied, 213
severity of retinopathy correlated, 315
status of retinopathy after, 315
stress of the procedure, 360
summary of results of, 216, 217
summary of results in 120 patients receiving, 224
technique, 355–359
cerebrospinal fluid withdrawal, 355, 356
chiasm, approach to the, 356
clip on hypothalamic end of pituitary stalk, 356
dural incision, 355
exposure, unilateral frontal, 355
gold foil implacement, 356
gold plate interposition, 356
heart-beat monitoring, 356
illustrated, 357, 358
incision, 355
optic nerve, elevation of, 355
pericranial incision, 355
spinal puncture, 355
stalk location, 358
wound closures, 359
urinary tract infections, and, 360
visual retention index, 219
wound infections, and, 360
Standard photographs, 11
Statistics
blindness and sex-specific rates, 43
blindness caused by diabetic retinopathy in England and Wales, 43–45
British-American comparison, 45
incidence increase in blindness since 1962 in England and Wales, 44
question on Beetham's, 99
statistical charts, Koehler's, 379
statistical followup information required on, 650
St. Bartholomew's Hospital, London, England, 55, 479
Steiner, R. E., 234, 373
Steiness, Ib., 310
Steno Memorial Hospital Gentofte, Denmark, 673, 680, 681
Sterility a secondary gain, 193
Stereotaxic apparatus used in pituitary suppression, design of, 251
Stereotaxic proton hypophysectomy, 253
see also Pituitary suppression
Stereotaxic radio frequency method for hypophysectomy, 274
see also Pituitary suppression
Stereotaxic transsphenoidal route for pituitary ablation, 416
Steroid excretion tests following radiation therapy, 283, 284, 285
Stressful states management following pituitary ablation, 229
Stewart, A. G., 567
Straatsma, Bradley R., XII, LVIII, 24, 428, 607–611, 613, 616, 617, 621, 637
Strandjord, N., 373
Straub, W., 681, 688
Stress
operative, in stalk section, 360
surgical, in hypophysectomy, extirpative, 341
Stress test, 400
response to, 400
Studies on diabetic and nondiabetic eyes, conclusions on, 673
illustrated, 674–679
Study comparison problems, 82
Subhyaloid hemorrhagic lesions, 16
Sublabial transnasal transsphenoidal hypophysectomy, 331, 332

Substitution therapy, 397
Sugimachi, Y., 689
Sugita, Y., 681, 688
Suicidal tendencies, 363
Suicides, few reported, 396
Sulphation factor, the, 401
Summary of data, 780–781
Summary of papers on ocular aspects of pituitary ablation, 375–379
Summary of papers on photocoagulation treatment techniques, 623–629
Summary of surgical aspects of pituitary ablation, 415–421
Summers, V. K., 663
Suppression, pituitary proton beam, by the, 249–276
Surgical aspects of pituitary ablation—discussion of, 422–434
Surgical hyphophysectomy in treatment of diabetic retinopathy, 193–202
Surgical probe allows tactile sensation, 433
Surgical procedure and management in pituitary ablation, 229–230
Surgical procedures in pituitary ablation illustrated, 200
Survival data—heavy-particle radiation following, 279–281
Survival following hypophysectomy related to extent of other vascular disease, 337
Survival statistics pituitary suppression by radiation, following, 279–281
Svien, 276, 353, 415, 418, 494
Sweet, William H., VI, X, XII, XIV, XIX, 195, 213–225, 252, 355–364, 375, 378, 412, 413, 415–421, 423, 424, 426, 430, 433, 715, 717, 722–729
Sydenham, 147
Symbols used to define neovascularization, 28
Symposium on Treatment of Diabetic Retinopathy, XIX
  classification scheme devised for, XXI
  impressions of state of diabetic retinopathy therapy at, XIX
  major deficiencies uncovered at, 721
  manuscripts summarization, XIX
  organization of, XIX
Symposium on Treatment of Diabetic Retinopathy—Continued
  sessions of, divided, XIX
  summarization of manuscripts, XIX
Systematic effect of pituitary ablation, 649
Szabo, A. J., 567

T

Talairach and Frazer's 1953 implantations, 149
Talairach, J., 365, 373
Tanabe, T., 688
Tani, M., 169
Target gland response evaluation, 398
Tassy, A. F., 681, 688
Taussky, H. H., 310
Taylor, E., 64, 484
Techniques of photocoagulation—discussion of, 630–653
Tendon reflexes following yttrium-90 implant, 320
Tension lines in macula, 85
Terminology used in assessment of disease after photocoagulation, 510, 512
Testosterone, 347
Testosterone enathate, 335
Testosterone isobutyrate, 294
Tests on diabetic and nondiabetic eyes, illustrated, 674–679
Teuscher, Arthur, 177, 191, 395, 399
Theoretical conclusion following observation of fluorescein circulation, 600
Therapy
  see also Pituitary ablation
  diabetic retinopathy, for, impressions of state of, XIX
  evaluation of, V, XXI, 3
  medical regimens in, XXI
  regimens, a multitude of, 22
  substitution, 294
Thermal changes as destructive mechanism in pituitary ablation, 150
Thermal procedures, 564
Thickening of posterior vitreous face, 57, 58, 59
Thomas, C. I., IX, XIII, 331–339, (Data) 762–767

Thornfeldt, Paul R., XVIII, 24, 462, 535, 543, 545, 555–562, 649
Thrombosis, venous, incipient, 617
Thyroid and adrenal function irradiation therapy, and, 288
Thyroid function, 220
autonomous, 404
evaluation, 203
studies, 242, 243
test, PBI, response of, 269
tests, 207
pituitary ablation, following, 333
pituitary function tests, and, 267
Thyroid replacement therapy, 230, 239–240, 285
Thyroxine, 320
Tissue hypoxia, suggested, 48
Tobacco Research Council (British), 78
Tobias, C. A., IX, 277–289, 715
Tolentino, F. I., 58, 64, 494, 514, 562
Tolstoi, Edward, 115, 117
Torack, R. M., 195, 202
Toronto General Hospital, Toronto, Canada, 521
Tournoux, P., 373
Toussaint, Daniel, 169
Toxi-infectious states, 360
Traction on retinal vessels, 57, 59
Traction on the retina, 51
Transfrontal hypophysectomy, 215
Transnasal approach to implantation for pituitary ablation, 230
Transnasal-transsphenoidal yttrium-90 implantation, 331
Transparencies for study of classification by photography note on, 22
Transparency, loss of, 50
Transsphenoidal
anterior pituitary ablation, 235–247
data on, 748–750
approach to pituitary ablation, 195
hypophysectomy, 294
microsurgical selective anterior pituitary ablation, 235–247
open operations summarized, 415
pituitary ablation, 692
"Treatable" eyes—1-year followup tabulations, 327
Treatment
choice of, or no treatment—poll of Symposium audience, 652
Treatment—Continued
comparisons, XX, 691–700
captions to figures in chapter, 694
comparison of methods, 699
conclusion, 699
data description, 691–692
eyes excluded from analysis, reasons for, 691–692
paper analyzed and results tabulated, 692
techniques of treatment listed, 692
visual acuity, and, 693
visual retention, long-term related to selection, 698
details in Mortimer's 64-patient photocoagulation series, 519–521
diabetic retinopathy, of, what are the choices?, 563
effective in proliferative diabetic retinopathy, 98
techniques and visual retention, 703
when to start?, 630, 631
Triglycerides, elevation of, 246
Triidothyronine, 333
Trypsin digestion techniques in monkey retinal examination, 665, 666
Tsuzuki, K., 688
Tyndall Effect, the, 620

U

UCLA School of Medicine, Los Angeles, Calif., 341, 537
photocoagulation and cryohypophysectomy at, 648
Udvarhelyi, George B., 564
Ultrasound laboratory at Columbia University, 635
Ultrasound
bending with prisms, 635
experiments with rabbits, 636
liquefication of vitreous by, 636
Undiagnosed diabetes, survey in England, 135
Unfitness for surgery, patient's proton-beam pituitary suppression, and, 249
Uniocular patients and photocoagulation, 614
University Eye Clinic, Copenhagen, Denmark, 495

University Hospital, Copenhagen, Denmark, 681
University of British Columbia, 485
University of California, 277
University of Kansas experiment, 411–412
University of Wisconsin Diabetic Retinopathy Clinic, 81
University of Wisconsin Medical School, Madison, Wis., 701, 704
University of Wisconsin Medical School study, 47–53
Uremia, 425
  preexisting, death caused by, 208
  terminal blindness, and, 265
Uric acid measurement in 200 diabetics, 389
Urinalysis, 229
Urinery FSH test, 174
Urinary protein, quantitative, evaluation, 229
Urinary steroid excretion test following metapyrone administration, 174
Urinary tract infections, 360
Urine testing and insulin administration, postoperative, 206
Urine testing for glycosuria threshold, 120
U.S. Atomic Energy Commission, 277
U.S. Public Health Service, XIX, 20, 227, 437, 485, 545, 559, 665, 718
U.S. Public Health Service Hospital, Baltimore, 641
U.S. Public Health Service Symposium, 691
  major aim of, a, 701
U.S. Series—difficulty of comparison with British series, 412
Usami, E., 683, 689
Uveitis, 241

V

Vaginal cornification, 397
Van Heuven, W. A. J., XI, XVI, 29, 36, 46, 507–514, 559–562, 609, 620, 624, 635
Vancouver General Hospital, 485
Vannas, S., 728
Vascular damage
  hypophysectomy, and, 291
  irreversible, 232
Vascular disease
  "all patients get it sooner or later", 139
  blood sugar, and, is there a relationship?, 144
  diabetes control, and, 129
  diabetes mellitus, and, 232
  diabetic, no explanation for, 150
  generalized, 63
  hypophysectomy for, 723
  pancreatic failure, and, 116
  peripheral, 445
    diabetes mellitus, and, 227
  risk of developing vascular disease same in young and old diabetics, 133
Vascular dynamics, changes in, photocoagulation causing, 641
Vascular hypertension and cotton-wool patches, 48
Vascular pressure concept, the, 663
Vascular pressure ratios in diabetic retinopathy, 657–663
Vascular tissue, diabetes mellitus affecting, 227
Vasopressin, 207, 403, 405
  radioimmunoassay for, 403
Vasoproliferation, 49, 537
Vein occlusion, 17
Venograms, cavernous sinus—reliability of in question, 368
Venous abnormalities, XXII, 12, 21
Venous changes following photocoagulation, 578
Venous dilatation in diabetic retinopathy, 49
Venous distension decreased by photocoagulation, 720
Venous irregularities, 3, 5
  classification and, 33–34
  evaluation variations in the Hammersmith system, 3
  grading of, yttrium-90 implants, following, 324
Venous occlusion in diabetic retinopathy, 49
Venous pressure, intraocular, normal, 657
Venous varicosities, 437
Venous thrombosis, incipient, 617
Vessel changes, functional reversible, 167

Vibration perception test, 293
Vibratory perception threshold test, 300
Visceral vascular changes, pituitary ablation inducing, 233
Vision
compromised by retinopathy, 631
loss, more than one factor producing, 512, 513, 565
lost in one eye and ocular status for hypophysectomy, 89
maintenance, 26
photocoagulation, at time of tabulated, 510
preservation, 593
"preserved," definition, 265
prognosis for, 41–43
age, and, 41
"retained or sustained" definition required, 692
retention, likelihood of, 693
return to "walking" vision, 632
spontaneous improvement in chances of, the, 100
undue emphasis on, 29
useful, 253
Visual results of treatments, 701–710
Visual acuity, 20, 26, 27, 33, 43, 61, 293, 318, 445, 486, 488, 595
accurate method of comparison, an, 33
age of patient, and, 573, 574, 575
average value before treatment, 698
changes in, 89, 489
photocoagulation, following, 209, 526, 527
charted, 253
Comparisons, preoperative and postoperative, 258, 260
criterion for judging results, a, 31
diabetic control, and, 125
distribution in 30-patient series, 303
divisions of, 20
functional classification, 31
grading of, yttrium-90 implant, following, 325
hemorrhages, and, 537
initial and final clinic visits recorded at, 81
lipid absorption and, 641
macular exudates, with, 612
misleading, extremely, 32
Visual acuity—Continued
normal subjects in, 682
percentages in all types of treatment, similar, 727
photocoagulation, and, 540, 541, 543, 572, 573, 574, 575
poor assessment of overall retinopathy, a, 328
preoperative, 332
pretreatment, 692
ratio (postoperative and preoperative), 258, 260
ophthalmological findings, versus summary of, 264
other ocular findings and, 260
relation of preoperative angiopathy and proliferation grades in 150 eyes, 261
versus pituitary function (139 eyes), 271
recording and followup necessary, 20
retained after 1 year or more, tabulated, 703
retention a criterion for "success," 701
retinopathy severity and, 508
satisfactory criterion for judging results, a, 82
Snellen chart, recorded by, 121
subjective, changes in after pituitary ablation, 207
yttrium-90 implants, following, 325
Visual and anatomic results of photocoagulation
discussion of, 612–622
summary of, 607–611
Visual field
before and after coagulation, 576
changes in, 303
defect
photocoagulation, ascribed to, 611
laser treatment and the, 644–645
Visual deterioration
correlated with severity of diabetic retinopathy, 90
hypophyseal stalk section, after, 314
natural course of, 88
proliferative and background retinopathy, in, 42
Vision duration in second eye following severe impairment of first eye, tabulated, 90

Visual impairment
degrees of, 437–438
diabetic retinopathy as a cause of, 41–46
progressive — pituitary ablation, and, 228
Visual improvement after hypophysectomy, 241
onset of, tabulated, 242
Visual loss
causes in 200 eyes tabulated, 85
from diabetic retinopathy, pathogenesis of, 559–562
photocoagulation cannot prevent in some cases, 610–611
pituitary suppression, indicating, 253
Visual prognosis
advanced diabetic retinopathy, in, 87–91
improvement, 210
natural history, and, discussion on, 99
proliferative retinopathy, and, 42
summary of papers on, 97–98
Visual results of treatments
pituitary ablation, following, 184
summarized, 377–378
summary, 710
systemic factors in, 702
table on visual retention, 703
Visual retention
index of, 219, 253, 267
cryohypophysectomy, following, 348
eye scoring by, 265–267
photocoagulation, following, 540, 541
results of 37 irradiation-treated patients, 287
proliferative diabetic retinopathy, in, 705, 708, 709
statistics, 63
232 patients series, in, 596
Visual status following pituitary ablation, 186
Visual symptoms a prognostic factor, 41
Vitamin B_{12}, 119
of no value, 119
Vitamins C and K, 81
Vitreous
architecture of, 29
abnormalities noted, 507
band, surgical division of, 59
biomicroscopic examination of, 721
blood in the, 559–560
blood classifications following photocoagulation, 511–512
blood classification tabulated, 560
blood, status after photocoagulation, 560
classification, 560
Van Heuven, of, 507
clearing following hypophysectomy, 383, 384
following pituitary ablation on objective sign, 652
phenomenon, the, 384
contraction, 617
detachment
partial, 560
posterior, 51
hemorrhage, XXI XXII, 254, 262, 264
classification, and, 36
grading of, 20
legal blindness, deterioration to, 97
liquification by ultrasound, 636
prognosis for vision, and tabulated, 43
worse than proliferative diabetic retinopathy, 99
retraction, 58
studies, 713
diabetic retinopathy treated with photocoagulation, 559–562
Vitroretinal adhesion, 560, 760
determining diabetic retinopathy prognosis, a factor in, 561
photocoagulation, disruption by, 473
photocoagulation may cause, 513
significance of, 562
Vitroretinal relationships, 8
Vitroretinal traction and photocoagulation, 512
Von Hippel's angiomatosis, 472

W

Walker, A. E., 151
Washington University School of Medicine, St. Louis, Mo., 523

Water intake, control of after pituitary ablation, 405
Water restriction, 717
Weidberg Foundation, Joseph M. and Evelyn R., 153
Welch, Robert B., XI, XVII, 563–568, 609, 719
Werner, A. U., XII, 673–680
Wessing, Achim K., XI XVIII, 169, 569–592, 609, 612, 613, 623, 624, 627 630
Wetzig, Paul C., XI, XII, XIII, XVIII, XXI, 7, 35, 188, 373, 462, 475, 477, 488, 494, 506, 514, 535, 543, 545, 553, 568, 592, 593–601, 609, 623, 627, 630–653, 692, 698, 700, 703, 714, 718, (Data) 828–851
White, Priscilla, 46, 202
Whittington, T. H., 46
Williams, R. H., 151
Williams, T. Franklin, 127, 128
Wilks, S. S., 700
Wilmer Institute, the 474, 564, 566
Winter, F. C., 494
Wisconsin University Department of Ophthalmology, 22
Wise, G. W., 48, 53, 466, 472, 477
Wolf, E., 620
Wolff, Stewart M., 564
Wolter, J. R., 64, 235, 247, 354, 410, 411, 727, 729
Wolter, neural mechanism hypothesis of, 246
Worlton, J. T., 506, 514, 543, 553, 592 601
Written descriptions in classifications, 11
Wulfing, B., 688

X

Xenon apparatus, 547
Xenon-arc and laser treatment, 636, 637
Xenon-arc photocoagulation, 188, 438, 461, 550, 551, 637
  disadvantages of, 438
  multiple applications, 453
  See also Zeiss
X-rays used for proton beam-pituitary target alignment, 250, 251
Xylocaine, 781

Y

Yaeger, 148
Yonemura, D., 688
Yttrium-90 implantations, 120, 149, 194, 195, 230, 308, 317–329, 416, 418, 423, 564, 692
  abandonment of, 419
  ablation achieved by
    intermediate, 318
    maximal, 318
    slight, 318
  acceptance for treatment requirements eased, 332
  anesthesia in, 332
  blood sugar level maintenance following, 327–328
  cerebrospinal fluid rhinorrhea prevention in, 332
  complications following, 321
  death during a second implant procedure, 335
  deaths unrelated to procedure, 321
  delayed complications incidence in, 341, 342
  endocrine ablation degrees achieved by, 317
  endocrine deficiency achieved by, 318
  endocrine followup, 320
  extraocular and ocular palsies following, 341
  followup results tabulated, 321–327
  groups abandoning the technique, 419
  hypoglycemia incidence following, 328
  hypopituritarism degrees produced by, 715
  impotence following treated by primotestone-depot, 320
  irreversible eye, and the, 319
  management following, 320
  medical followup, general, 320, 327
  menstruation records following, 320
  method of study of 100 patients, 318–321
  morbidity following, 195, 321, 335
  patient selection for, 329
  pituitary ablation, in, 227
  sex function following, 320
  soft exudates, and—illustrated, 382
  studies in series of 100 implants of, 317–329

Yttrium—Continued
studies of 60 patients—1967 results, 317
studies of 38 patients—1965 results, 317
technique of, 331
treatable eye, and the, 319
transsphenoidal, 395
nephropathy, death from, and, 328
ophthalmologic followup, 319
ophthalmologic response to index of, 323–324
radiofrequency ablation, compared with, 372
results of series study, 321–328
rhinorrhea, cerebrospinal, and, 342
rhinorrhea complicating use of, 365
rhinorrhea following, 335
varying degrees of pituitary ablation, 317
Yttrium—Continued
vision stabilization after, 725

Z

Zeiss fundus camera, 10, 121, 154, 441
Zeiss motorized slit lamp, 293, 441
Zeiss of Jena, East Germany, 551
Zeiss ophthalmoscope, 293
Zeiss photocoagulator, 480, 495, 507, 510, 519, 523, 566, 594, 623, 641
versus ruby laser type, 556
Zeiss xenon photocoagulator, 470, 487, 569
Zervas, Nicholas T., IX, X, XIII, XVIII, 150, 202, 203–212, 353, 365–373, 377–378, 416, 420, 425, 429, 433, 434, (Data) 739–742
Zweng, H. Christian, XI, XVIII, 442, 462, 603–605, 614, 627, 636–637, 638, 646–647, 671, 714

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